Washington State Health Care Authority

Health Technology Assessment

Hyperbaric Oxygen Therapy (HBOT) for Tissue Damage, Including Wound Care and Treatment of Central Nervous System (CNS) Conditions

DRAFT REPORT

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A Health Technology Assessment

Prepared for Washington State Health Care Authority

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EXECUTIVE SUMMARY

Background

Hyperbaric oxygen therapy (HBOT) involves the systemic administration of 100% oxygen while the patient is inside a treatment chamber under pressures > 1 atmosphere absolute (ATA). Hyperbaric oxygen was introduced as a medical treatment more than 200 years ago and has been advocated as a treatment for a wide variety of conditions over the years. Despite a large body of published literature, it remains unclear as to the indications for which HBOT is most effective and safe. Among the indications for which questions still remain are diabetic nonhealing wounds, including foot ulcers; other nonhealing wounds, including skin and tissue grafts, thermal burns, and surgical wounds; refractory osteomyelitis; late radiation tissue injury (LRTI); brain injury; cerebral palsy; headache and migraine; multiple sclerosis; and sensorineural hearing loss.

Foot wounds are one of the most common complications of diabetes and are responsible for substantial morbidity. At any given time, lower extremity ulcers affect approximately 1 million diabetics. HBOT is used along with traditional systemic and topical therapies to promote diabetic wound healing. It is purported to reverse anaerobic infection, improve blood supply, and reduce ischemic nerve damage.

Chronic wounds other than those related to diabetes include venous and pressure sores, with causes that are related to venous insufficiency, pressure, trauma, vascular disease, and immobilization. Although the causes of chronic wounds vary, in all cases, at least one of the phases of wound healing is compromised.

Surgical wounds present a medical problem if they are large in size, especially if bones and tendons are exposed and therefore are not amenable to primary closure. By increasing the oxygen tension in hypoxic wounds, HBOT is thought to restore the level of oxygenation required for compromised tissue to function efficiently. HBOT is also proposed as a means of preparing a base for skin grafts and flaps or preserving compromised grafts and flaps.

Thermal burns are the third largest cause of accidental death, with 300,000 serious burns and 6000 fatalities occurring annually in the United States. HBOT for thermal burns is directed at enhancing host defenses, preserving marginally viable tissue, protecting the microvasculature, augmenting neovascularization, and promoting wound closure.

Chronic osteomyelitis can develop when bacterial or fungal infection within bone deprives the bone of its blood supply, and the resulting ischemia causes bone tissue necrosis. It has been hypothesized that the additional oxygen delivered during HBOT may promote collagen synthesis and angiogenesis in patients with hypoxic osteomyelitic wounds.

More than 1.4 million Americans are diagnosed with cancer each year, and approximately half of these patients receive radiation therapy as part of their management. Radiation side effects can be categorized as either acute or delayed (chronic) complications; the latter may develop months or years after radiation treatment and collectively are known as late radiation tissue injury (LRTI) or late radiation side effects. Although any tissue may be affected, late radiation tissue injury occurs most commonly in the head and neck, chest wall, breast, and pelvis, reflecting the anatomical areas most commonly irradiated. Chronic radiation damage is called *osteoradionecrosis (ORN)* when bone is damaged and *soft*

tissue radionecrosis when muscle, skin, or internal organs have been damaged. Evidence continues to emerge as to the effectiveness of HBOT for the treatment of LRTI, including ORN.

The use of HBOT for chronic brain injury is based on a theory that oxygen availability to these cells stimulates the cells to function normally, reactivating them metabolically or electrically. HBOT has also been investigated as a treatment for traumatic brain injury (TBI), which accounts for more than 1.3 million emergency room visits, approximately 275,000 hospitalizations, and 52,000 deaths annually.

Cerebral palsy is a neuromuscular disorder that arises in children due to damage of the developing brain. This disorder occurs in 0.1% to 0.5% of live births and is characterized by impairments of muscle control, the senses, and perception. There is no known cure for cerebral palsy; the usefulness of HBOT for the treatment of cerebral palsy relates to the possibility of restoring function in portions of the brain that have suffered damage due to lack of oxygenation or other trauma.

More than 45 million individuals in the United States suffer from chronic, recurring headaches. Approximately 90% of headaches are primary headaches, which do not arise from an underlying medical condition. Cluster headaches are quite rare and occur in only 0.1% of the population. Migraine headache affects more than 28 million individuals in the United States and more than 300 million individuals worldwide. The theory is that HBOT might favorably influence vascular headache resistant to conventional drug therapy.

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) that afflicts an estimated 400,000 individuals in the United States and more than 2.5 million worldwide. The use of HBOT as a treatment for MS was originally based on the demonstrated ability of HBOT to produce vasoconstriction with increased oxygen delivery and some anecdotal evidence of efficacy. For several years, there was a flurry of investigation into its effectiveness for the treatment of MS, which produced a number of randomized studies in the UK, U.S., and Europe.

Sudden sensorineural hearing loss (SSHL), or sudden deafness, is a rapid loss of hearing with onset over a period of less than 72 hours. The estimated incidence of SSHL ranges from 5 to 20 per 100,000 persons per year but may be as high as 300 per 100,000 persons per year. HBOT has been proposed for the treatment of SSHL, the rationale being that the hearing loss appears to be caused by a hypoxic event in the cochlear apparatus; therefore, HBOT may potentially reverse the oxygen deficit, increase oxygen pressures in the cochlea, and improve microcirculation. Proving the effectiveness of HBOT for SSHL is complicated given the fact that up to two thirds of SSHL cases resolve spontaneously (Mattox and Simmons, 1977).

Technology Description

HBOT involves the therapeutic administration of 100% oxygen at environmental pressures > 1 ATA, the atmospheric pressure at sea level. Administering oxygen at pressures greater than 1 ATA requires compression. This is achieved by placing the patient in an airtight chamber. The pressure is increased inside the chamber, and 100% oxygen is given for respiration, which delivers a greatly increased pressure of oxygen to the lungs, blood, and tissues.
There are 2 types of chambers used for administering HBOT: a monoplace chamber for a single patient; or a multiplace chamber used for multiple patients and medical personnel. No standard protocol has been identified for administering HBOT.

Key Questions

1. Is HBOT effective in improving patient-centered outcomes for individuals with the following conditions:
- Diabetic nonhealing wounds, including foot ulcers
- Other nonhealing wounds, including skin and tissue grafts, thermal burns, and surgical wounds
- Refractory osteomyelitis
- Late radiation tissue injury (LRTI)
- Brain injury
- Cerebral palsy
- Headache/migraine
- Multiple Schlerosis (MS)
- Sensorineural hearing loss

1a. What is the optimal frequency, dose, and duration of HBOT treatment?

2. What harms are associated with HBOT?
3. What is the differential effectiveness and safety of HBOT according to factors such as age, sex, race or ethnicity, disability, comorbidities, wound or injury duration and severity, and treatment setting?
4. What are the cost implications of HBOT, including the cost-effectiveness compared with alternative treatments?

Methods

Search Strategy and Selection of Evidence

A detailed analysis of all relevant primary data for each indication under investigation was beyond the scope of this review. Consequently, we conducted a systematic search for systematic reviews and health technology assessments (HTAs) to answer each key question. In addition, we systematically searched for primary data published subsequent to the selected systematic reviews for each indication, as well as a search for all harms studies published over the last 10 years. All included systematic reviews were manually searched for additional relevant studies meeting the inclusion criteria. The databases searched included MEDLINE, the Cochrane Library, the York University Center for Reviews and Dissemination (CRD), and Embase. The results were limited to human studies in the English language published between 2002 and June 2012. An update search for randomized controlled trials (RCTs) and meta-analyses was conducted in November 2012.

Search Strategy and Selection of Guidelines/HBOT Coverage Policies

In addition to guidelines found through the database and manual searches outlined above, we also searched the National Guidelines Clearinghouse, and, at the direction of Washington State Health Care Authority (HCA), we searched the Centers for Medicare & Medicaid Services (CMS), Aetna, Regence Blue Cross Blue Shield (BCBS), and Group Health Cooperative websites for coverage-policies relevant to this report. In addition, we searched the Hayes Knowledge Center for relevant reports, which were used as

background to identify primary data studies not included in the selected published systematic reviews and as a source of harms data.

Quality Assessment

We conducted quality assessments throughout the process. We rated the quality of each systematic review using the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Shea et al., 2007). We employed Hayes quality methods for assessing the quality of primary studies and bodies of evidence (see Appendix II). Internally developed Quality Checklists for individual studies address study design, integrity of execution, completeness of reporting, and the appropriateness of the data analysis approach. Individual studies are labeled as *good*, *fair*, *poor*, or *very poor*. The Evidence-Grading Guides assure that assessment of bodies of evidence takes into account not only methodological quality in individual studies, but also the applicability of bodies of evidence to the population(s), intervention(s), and health outcome(s) of interest; the consistency and precision of results across studies; and the quantity of data (number of studies and sample sizes). The quality of the bodies of evidence for particular outcomes is labeled as *high*, *moderate*, *low*, or *very low*.

The Appraisal of Guidelines Research and Evaluation (AGREE) (AGREE Enterprise, 2012) tool was used to assess the quality of practice guidelines.

Search Results

We found 21 systematic reviews meeting predefined inclusion criteria. Also included are 4 harms-specific primary data studies; and 6 primary data studies covering a range of indications of interest and identified through a search for studies published subsequent to the included systematic reviews. In all, the report includes findings from 156 primary data studies. Several reviews were cross-cutting in nature, covering more than one indication or Key Question.

Findings, Key Question #1: Is HBOT effective in improving patient-centered outcomes for individuals with the following conditions:

Diabetic nonhealing wounds, including foot ulcers
Other nonhealing wounds, including skin and tissue grafts, thermal burns, and surgical wounds
Refractory osteomyelitis
Late radiation tissue injury
Brain injury
Cerebral palsy
Headache/migraine
Multiple sclerosis
Sensorineural hearing loss

Sixteen systematic reviews (133 primary data studies) plus an additional 5 primary data studies, published subsequent to the chosen reviews, were selected to answer KQ1, bringing the total number of included primary data studies to 138 (7225 participants). Of the included studies, 61 were RCTs, 4 were nonrandomized controlled trials, 8 were pre-post studies (7 uncontrolled, 1 with historical controls), and 64 were other observational studies, including prospective and retrospective cohorts as well as case series.

HBOT for Diabetic Nonhealing Wounds, Including Foot Ulcers

Three systematic reviews (1437 participants), including 16 peer-reviewed studies (8 RCTs, 2 nonrandomized controlled trials, and 6 observational studies), reported on the effectiveness of HBOT for the treatment of diabetic nonhealing wounds. All of the studies involved diabetic foot ulcer patients and the outcomes evaluated included incidence of healing, wound size reduction, amputation rates, and quality of life (QOL).

Incidence of healing: Moderate-quality evidence from 12 studies (1 good, 4 fair, 5 poor, 2 very poor quality) suggests that the addition of HBOT to standard wound treatment substantially improves healing among patients with nonhealing diabetic foot ulcers. The strongest evidence comes from a good-quality 2012 Cochrane Review, which pooled data from 3 trials (140 participants) and found a strong effect on healing at 6 weeks (relative risk [RR], 9.53; 95% confidence interval [CI], 0.44-207.76; number needed to treat [NNT], 8), which was no longer significant at 1 year.

Amputation rates: Seven studies (1 good, 3 fair, and 3 poor quality) provide moderate-quality evidence that the addition of HBOT to standard wound treatment reduces the risk of amputation. The 2012 Cochrane Review pooled data from 5 trials (309 participants) and showed a trend toward a benefit from HBOT in the rate of major amputations, but no statistically significant difference between the groups (RR, 0.36; 95% CI, 0.11-1.18). One of the 5 included studies excluded participants at high risk for major amputations, and when this study was excluded from the analysis, the benefit of HBOT became significant (*P*=0.009). HBOT provided no additional benefit in the rate of minor amputations. Observational data from other reviews found HBOT to be an effective adjunct treatment for the reduction of amputations among diabetic patients with nonhealing wounds.

Wound size reduction and QOL: Evidence for the effectiveness of HBOT for wound size reduction and QOL is of very low and low quality, respectively. A 2012 Cochrane Review found just one fair-quality RCT,(n=28) which reported a 41.8% reduction in wound size at 2 weeks posttreatment among the HBOT group compared with 21.7% in the control group (*P*=0.04), the effect of which was no longer significant at 4 weeks. Similarly, 1 good-quality RCT (n=94) found no significant difference in overall physical summary scores between the HBOT and control groups at 1-year follow-up (mean difference [MD], –0.2; 95% CI, –8.58 to 8.18), and no significant difference in overall mental health summary scores (MD, 6.60; 95% CI, –3.93 to 17.13).

Quality assessment and summary: Moderate-quality evidence from 3 systematic reviews (1437 participants), including 16 peer-reviewed studies reporting on the effectiveness of HBOT for the treatment of diabetic foot ulcers, suggests that the addition of HBOT to standard wound care promotes wound healing and limb salvage in the short term, with no improvement evident beyond 1 year. The results are clinically meaningful, with pooled data from 3 studies suggesting that 8 patients would need to be treated with HBOT as an adjunct to standard wound care for an additional 1 person to have complete wound healing. There is insufficient evidence to determine the effect of HBOT on wound size reduction and low-quality evidence suggesting no benefit from HBOT on QOL measures.

Summary of evidence by outcome for HBOT as a treatment for diabetic nonhealing wounds, including diabetic foot ulcers

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Incidence of healing	Benefit at 6 weeks, not significant at 1 year	1 good, 4 fair, 5 poor, 2 very poor	Moderate
Amputation rates	Benefit	1 good, 3 fair, 3 poor	Moderate
Wound size reduction	Benefit at 2 weeks, not significant at 4 weeks	1 fair	Very low
Quality of life	No benefit	1 good	Low

HBOT for Other Nonhealing Wounds, Including Skin and Tissue Grafts, Thermal Burns, and Surgical Wounds

Five systematic reviews (776 participants), including 16 peer-reviewed studies (7 RCTs, and 9 observational studies) reported on the effectiveness of HBOT for the treatment of nondiabetic nonhealing wounds. Wounds included arterial, pressure, and venous ulcers; flaps and grafts; crush injuries; surgical reconstruction (without grafts or flaps); and thermal burns. The outcomes evaluated include incidence of healing, time to healing, reduction in wound size, amputation rates, survival of flap or graft, length of hospital stay, mortality, and number of surgeries.

Incidence of healing or reduction in wound size among patients with venous, arterial, or pressure ulcers: Low-quality evidence from 4 studies (2 fair and 2 poor quality), including 51 patients, reported on the incidence of healing or wound size reduction among patients with ulcers. One small, fair-quality RCT (n=16) found a significant reduction in venous wound area among patients receiving HBOT versus controls at 6 weeks follow-up (MD, 33%; 95% CI, 18.97-47.03) but no difference at 18 weeks and found no significant difference between groups in the proportion of ulcers completely healed at any time. A small, poor-quality case series of 35 patients with leg ulcers reported 80% compete wound healing following HBOT. The update search uncovered a very recent small RCT of fair quality, including 30 patients with a variety of ulcer types randomized to HBOT plus conventional treatment or conventional treatment alone. Following 30 days of treatment, there was a 59% reduction in wound area in the HBOT group compared with a 26% increase in wound area in the control group.

Incidence of healing, time to healing and amputation rates among patients with crush injuries: Very-low-quality evidence from 1 fair-quality RCT of 36 patients with crush injuries found significantly more complete healing among the HBOT group (94%) compared with controls (56%) (RR, 1.7; 95% CI, 1.11-2.61; NNT, 3), but no significant difference between groups with regard to mean time to healing, number of amputations, and mean length of hospital stay.

Incidence of healing among patients having undergone surgical reconstruction (without grafts or flaps): Low-quality evidence from 2 fair-quality prospective cohort studies (84 patients) suggests that HBOT may improve healing and reduce infection among patients having undergone surgical reconstruction (without grafts or flaps). One study reported 89% improved healing in the HBOT group versus 73% among controls ($P<0.05$); the other reported breakdown and infection in 1 patient receiving HBOT (17%) versus 7 patients (78%) not receiving HBOT ($P<0.01$).

Graft and flap survival/take and healing: Low-quality evidence from 7 studies (6 poor quality and 1 of unknown quality due to poor reporting) suggest that HBOT may be beneficial for the treatment of compromised skin grafts or flaps, but the results were not consistent. A 2010 Cochrane Review included

2 poor-quality RCTs, which examined the effectiveness of HBOT for improving graft or flap survival among patients with acute surgical and traumatic wounds. One looked at HBOT versus usual care for split skin grafts (n=48) and found significantly better graft survival among the HBOT group (64%) compared with the usual care group (17%) (RR, 3.5; 95% CI, 1.35-9.11; NNT, 2). The other found that HBOT was no better than dexamethasone for complete flap survival (89% versus 78%, respectively), and no better than local heparin for complete flap survival (89% versus 73%, respectively). A 2009 systematic review included 3 poor-quality case series (47 patients) evaluating graft take among patients having undergone HBOT before and /or after skin grafting and 1 poor-quality case series of 15 patients having received HBOT as an adjunct treatment for compromised flaps. One reported 50% complete graft take at 18-month follow-up, 2 reported 100% graft take, and 1 reported complete flap healing. In addition, a 2003 systematic review included an unpublished, unknown-quality RCT (160 patients), which reported more delayed wound healing among controls compared with those receiving HBOT (RR, 0.2; *P*=0.001).

Mortality, mean time to healing, graft take, number of required surgeries, and length of hospital stay among patients with thermal burns: Very-low-quality evidence from 2 fair-quality RCTs reported mixed results on the effectiveness of HBOT among 141 patients with thermal burns. After adjusting for the patients' condition, one trial found no significant differences in length of hospital stay, mortality (11% in each group), or number of surgeries between the HBOT and control groups. The other trial reported significantly better time to healing among the HBOT group (19.7 days) compared with the control group (43.8 days) (*P*<0.001).

Incidence of wound recovery and healing among patients with acute traumatic peripheral ischemia: Very-low-quality evidence from one systematic review reported one case series, which found improved wound recovery and complete healing among a series of 23 patients who received HBOT as an adjunct therapy.

Quality assessment and summary: Overall, there is limited low-quality evidence from 14 peer-reviewed studies, suggesting that HBOT may improve healing when employed as an adjunct treatment for venous ulcers, flaps and grafts, and surgical reconstruction (without grafts or flaps). We currently have low confidence in the reported estimate of effects for these conditions and the reported benefits should be interpreted with caution. In addition, there is insufficient evidence from 1 study to determine the effectiveness of HBOT for crush injuries, insufficient evidence (primarily due to mixed results) from 2 studies to determine if HBOT is effective for the treatment of thermal burns, and insufficient evidence from 1 study to determine the effectiveness of HBOT for the treatment of acute traumatic peripheral ischemia.

Summary of evidence by wound type for HBOT as a treatment for other (nondiabetic) nonhealing wounds

Wound Type	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Venous, arterial, and pressure ulcers	Short-term benefit	2 fair, 2 poor	Low
Compromised grafts and flaps	Benefit	6 poor, 1 unknown	Low
Surgical reconstruction (without grafts or flaps)	Benefit	2 fair	Low
Crush injuries	Mixed	1 fair	Very low
Thermal burns	Mixed	2 fair	Very low
Acute traumatic peripheral ischemia	Benefit	1 poor	Very low

HBOT for Refractory Osteomyelitis

Three systematic reviews (all of fair quality) (510 participants), including 23 peer-reviewed studies (0 RCTs, 2 nonrandomized controlled trials, and 21 case series), reported on the effectiveness of HBOT for the treatment of refractory osteomyelitis. The outcomes evaluated included resolution/cure, recurrence, and hospital stay.

Many very-poor-quality case series have been published over the years, all suggesting adjunctive HBOT as an effective cure for osteomyelitis. The median cure rate among 21 included case series (450 participants) was 87% (range, 37% to 100%), and the mean data from 5 very-poor-quality case series suggest a 5.4% relapse rate among 74 patients. One fair-quality nonrandomized controlled trial included in a 2012 systematic review supports these findings and represents the best-quality available evidence on the effectiveness of HBOT for osteomyelitis. That study reported significantly lower infection relapse rates among the HBOT group versus controls (0% versus 33.3%, respectively; *P*=0.024), and significantly fewer days in the hospital (52.6 days in the HBOT group [SD, 9.1] versus 73.6 days [SD, 24.5] among controls; *P*=0.026). In contrast, however, a poor-quality nonrandomized controlled trial (28 participants) reported by all three systematic reviews found no benefit from HBOT as an adjunct treatment to surgery and antibiotics for curing refractory osteomyelitis (*P*=0.28) and no difference in relapse rates between groups (*P*=0.54).

Summary and quality assessment: Low-quality evidence from 23 primary data studies (1 fair quality, 1 poor quality, 21 very poor quality) suggests that HBOT may be effective as an adjunct treatment for refractory osteomyelitis but we have low confidence in the reported estimate of effects. There is some evidence from one small, fair-quality, nonrandomized trial that HBOT may reduce the rates of relapse infection. Further good-quality studies are necessary to determine the effectiveness of HBOT for the treatment of refractory osteomyelitis.

Summary of evidence by outcome for HBOT as a treatment for refractory osteomyelitis

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Resolution/cure	Benefit	1 poor, 21 very poor	Very low
Infection relapse rate	Mixed	1 fair, 6 poor	Low
Number of days in the hospital	Benefit	1 fair	Very low

HBOT for Late Radiation Tissue Injury

Four systematic reviews (1628 participants), including 34 peer-reviewed studies (12 RCTs, 3 prospective cohorts, 6 retrospective cohorts, and 13 case series) plus 1 fair-quality RCT (36 participants) published subsequent to the systematic reviews, reported on the effectiveness of HBOT for the treatment of LRTI, including osteoradionecrosis (ORN) and soft tissue radionecrosis. A wide variety of outcomes were evaluated, including complete resolution or improvement of tissue damage or necrosis; prevention of ORN; late sequelae (LENT-SOMA scores); QOL; complete mucosal cover for ORN; establishment of bony continuity; healing of tooth sockets; loss of dental implants; and wound dehiscence.

Complete resolution or improvement of tissue damage or necrosis: Moderate-quality evidence from 18 studies (2 good, 2 fair, and 14 poor quality) suggests that HBOT significantly improves tissue damage and necrosis resulting from LRTI. A 2012 Cochrane Review reported pooled data from 4 RCTS, which looked at the complete resolution of tissue damage or necrosis at or before 3 months follow-up across all anatomical areas studied (325 participants). Overall, 36% of participants in the HBOT group and 28% in

the control group achieved complete resolution. There was, however, significant heterogeneity between the trials (I^2=82%) and no overall estimate of effect was provided. Individually, 2 trials reported a benefit from HBOT (1 significant and the other a nonsignificant improvement), and 2 found no additional benefit from HBOT over the controls. When complete resolution was combined with significant improvement of tissue damage or necrosis, there was a significant benefit to HBOT among patients with radiation proctitis (RR, 1.72; 95% CI, 1.0-2.9). A fair-quality RCT, published subsequent to the included systematic reviews, found that HBOT and intravesical hyaluronic acid both aided recovery among patients with radiation-induced hemorrhagic cystitis, reporting 75% complete recovery (defined as no symptoms) in the HBOT group at 6 months, 50% at 12 months, and 45% at 18 months. Finally, a 2003 systematic review of observational data reported 50% to 100% improvement in complete or partial healing of soft tissue radionecrosis among 168 patients treated with HBOT across 13 poor-quality case series.

Prevention of ORN following tooth extraction in an irradiated field: Moderate-quality evidence from 9 studies (1 fair, 1 unclear, and 7 poor quality) suggests that HBOT is effective in the prevention of ORN. One RCT reported a 5.4% incidence rate for the development of ORN following HBOT versus 29.9% among controls (RR, 0.18; *P*=0.005). The data were from an RCT of unclear quality, which looked at the effectiveness of HBOT to prevent ORN among patients who had been exposed to radiation of the head and neck and needed a hemimandibulectomy. In addition, 2 systematic reviews (including observational studies) reported an overall incidence rate of 7% for ORN among post-radiated head and neck cancer patients versus 4% among patients having received HBOT.

Complete mucosal cover and establishment of bony continuity: Moderate-quality evidence from 3 pooled studies (246 participants) (1 fair and 2 unclear quality due to poor reporting) reported significant benefit from HBOT in terms of achieving complete mucosal cover among patients with ORN (RR, 1.3; 95% CI, 1.1-1.6) and significant benefit from HBOT in terms of establishing bony continuity (RR, 1.5; 95% CI, 1.1-1.8).

Quality of life: Moderate-quality evidence from 5 studies (287 participants) (2 good and 3 fair quality) suggests that HBOT improves QOL among patients with LRTI induced by head and neck and bowel cancer but not among patients with axillary-related tissue injury. A significant benefit of HBOT was found for improvement in bowel bother subscale among patients with radiation proctitis (pre-post mean improvement, 14.1% in the HBOT group (*P*=0.0007) versus 5.8% in the control group (*P*=0.15), global QOL score among patients with dental implants in irradiated regions (MD, 17.6 points; 95% CI, 2.8-32.2), and 12-month QOL functional outcomes among patients with radiation-related damage following head and neck cancers. No significant benefit of HBOT was seen for general health at 12 months (weighted MD, –2.3; 95% CI, –19 to –14.4), physical functioning at 12-months (weighted MD, –4.0; 95% CI, –19.4 to 11.4) or lymphedema-specific functioning (*P*=NS) among patients with axillary-related tissue injury.

Improvement in late effects of radiation (LENT-SOMA scores): Low-quality evidence from 1 good-quality study (150 participants) found a significantly greater improvement in LENT-SOMA scores (an indication of improvement in late effects of radiation) in the HBOT group (MD, 2.4; *P*=0.002) at completion of treatment.

Loss of dental implants: Very-low-quality evidence from 1 fair-quality trial found that the risk of losing an implanted tooth following implant into an irradiated mandible was 2.5 times greater in the HBOT group versus controls, but this was not statistically significantly (RR, 2.5; *P*=0.22).

Wound dehiscence: Low-quality evidence from pooled data from 2 RCTS (368 participants, with unclear risk of bias due to poor reporting) found a significant benefit from HBOT in terms of reducing wound dehiscence (RR, 4.2; 95% CI, 1.1-16.8).

Quality assessment and summary: There is moderate-quality evidence from 35 primary data studies suggesting that HBOT improves outcomes of LRTI affecting bone and soft tissues. There is no overall estimate of effect because of the heterogeneity between studies, but the evidence suggests that radiation-induced tissue and bone damage to the head and neck, anus, and rectum show consistent clinical improvement with HBOT.

There is also moderate-quality evidence that HBOT reduces the risk of developing ORN following tooth extraction in a previously irradiated area.

Summary of evidence by outcome for HBOT as a treatment for LRTI

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Complete resolution or improvement of tissue damage or necrosis	Benefit	2 good, 2 fair, 14 poor	Moderate
Prevention of osteoradionecrosis (ORN) after tooth extraction	Benefit	1 fair, 7 poor, 1 unclear	Moderate
Complete mucosal cover and establishment of bony continuity for osteoradionecrosis (ORN)	Benefit	1 fair, 2 unclear	Moderate
QOL	Radiation proctitis: Benefit Radiation injury resulting from head and neck cancers: Benefit Patients with dental implants in irradiated area: Benefit Axillary radiation injury: No benefit	2 good, 3 fair	Moderate
Improvement in late effects of radiation (LENT-SOMA scores)	Benefit	1 good	Low
Loss of dental implants	No benefit	1 fair	Very low
Wound dehiscence	Benefit	2 unclear	Low

HBOT for Brain Injury

Two good-quality systematic reviews, including 16 studies (6 RCTs, 4 uncontrolled pre-post studies, 6 other observational studies) plus 1 additional fair quality pre-post study (63 participants) of relevance, but not included in either systematic review, reported on the effectiveness of HBOT for the treatment of brain injury, including TBI and other brain injuries. Outcomes evaluated included mortality and functional outcomes.

Mortality and functional outcomes among TBI patients: Moderate-quality evidence from the pooled data of 4 fair-quality trials (387 TBI patients) reported a significantly reduced risk of dying among TBI patients receiving HBOT versus controls (RR, 0.69; 95% CI, 0.54-0.88; NNT, 7).). The number of HBOT sessions varied from 10 to 40. Enrolment into the study following hospital admission varied across the studies. Rockswold (1992) reported enrollment after 6 hours; Xie (2007) reported enrollment after 24 hours; Artru (1976) reported enrollment after 4.5 days, and Holbach (1974) did not specify any period before entry into the study.

Moderate-quality data also from the pooling of 4 trials (382 TBI patients) (3 fair quality, 1 poor quality) found no significant reduction in the risk of an unfavorable functional outcome 1 year following HBOT (RR, 0.51; 95% CI, 0.25-1.08). There was significant heterogeneity between the trials (I^2=81%) and the results were borderline sensitive to the number of dropouts in one of the trials.

Mortality, functional outcomes, and symptoms among patients with non-TBI brain injury: Very-low-quality data were available in relation to non-TBI brain injuries. One poor-quality pre-post study (136 patients) found 7% mortality among patients following HBOT. A poor-quality, uncontrolled, observational study (32 patients) reported 5% to 10% improvement in memory among patients having undergone HBOT. Similarly, a poor-quality pre-post test, with historical controls, found both children and adults with chronic brain injury (including cerebral palsy, stroke, TBI, anoxic ischemic encephalopathy, and Lyme disease) had significantly improved cognitive performance following HBOT than did brain injured or normal controls. We have very low confidence in the reliability of these results; particularly since the treatment group showed significantly poorer cognitive performance before testing than did the brain-injured controls, increasing the likelihood for selection bias. Furthermore, the authors gave no explanation for the significant pre-post test difference observed among the normal controls. A number of other very poor or poor-quality studies reported high cure rates or improved symptoms among brain-injured patients having undergone HBOT, all of which had significant methodological flaws rendering the results unreliable.

Quality assessment and summary: Moderate-quality evidence from 10 primary data studies suggests that although HBOT may reduce the risk of dying following a TBI, there is little evidence that those who survive have a good functional outcome. Based on the available data, the review authors did not recommended routine application of HBOT to TBI patients

Evidence from 6 poor or very-poor-quality primary data studies are insufficient to determine if HBOT is effective in improving health outcomes among patients with brain injuries other than TBI.

Summary of evidence by outcome for HBOT as a treatment for brain injury

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Mortality among patients with traumatic brain injury (TBI)	Benefit (i.e. reduced risk of dying but with no evidence of improved function upon survival)	4 fair	Moderate
Functional outcomes among patients with TBI	No benefit	3 fair, 1 poor	Moderate
Mortality among patients with non-TBI brain injuries	Unknown benefit	1 poor	Very low
Functional outcomes among non-TBI brain injury patients	Benefit	2 poor	Very low
Symptoms among non-TBI brain injury patients	Benefit	1 poor, 2 very poor	Very low

HBOT for Cerebral Palsy

One good-quality 2007 systematic review (449 participants), including 6 studies (2 RCTs, 4 observational studies) (449 participants) reported on the effectiveness of HBOT for the treatment of cerebral palsy. The outcomes evaluated included motor function (change in gross motor function measure [GMFM] and % improvement in GMFM); caregiver assessment (using the Pediatric Evaluation of Disability Inventory [PEDI]); and other disease-specific outcomes such as improvement in speech, social functioning, and cognitive ability.

Motor function: Low-quality evidence from 1 fair-quality RCT and 2 fair-quality observational studies reported results on motor function. The results were mixed. The RCT reported improvements in GMFM among both the HBOT and control groups, with no significant difference between the groups immediately following treatment and again at 6 months follow-up (mean change in GMFM immediately posttreatment was 2.9 in the HBOT group versus 3.0 in the control group, P=NS; mean change at 6 months follow-up was 3.4 in the HBOT group versus 3.1 in the control group, P=NS). Two small (n=25 and n=7) prospective before-after studies both reported improvements in GMFM among patients receiving HBOT (5.3% and 8.9% improvement in GMFM scale, respectively).

Caregiver outcome: The evidence related to caregiver outcomes was of low quality overall. Two RCTs (1 fair quality, 1 poor quality) reported on caregiver outcomes. One fair-quality RCT found that the control group had significantly better mobility and social functioning posttreatment (data not provided). A poor-quality RCT reported no difference between groups in PEDI scores according to the results from blinded assessors but found a significant improvement in PEDI mobility subscore favoring HBOT among unblinded parents (data not provided).

Other outcomes: The overall quality of the data for all other outcomes was considered very low. A poor-quality prospective time-series of 50 patients reported improvements of 13% for motor, 6% for cognitive, and 7% for speech abilities 2 days post HBOT. Another poor-quality retrospective time-series (230 participants) reported 95% reduced spasticity immediately post HBOT, which persisted among 76% of 82 children at 6 months follow-up. There was a high risk of bias among both of these studies.

Quality assessment and summary: There is insufficient evidence from 6 studies (2 RCTS and 4 observational studies) to determine the effectiveness of HBOT for the treatment of cerebral palsy. Inconsistencies in the direction of the results, a paucity of studies, small sample sizes, differences in baseline characteristics, and the number of treatment sessions provided, all contributed to the low-quality grade assigned to motor function, which was considered the major outcome of interest. Fair- to poor-quality observational data suggests an improvement in motor function and other disease-specific subjective outcome measures among children receiving HBOT, but a fair-quality RCT found no additional benefit from HBOT among children receiving HBOT versus those receiving pressurized air.

Summary of evidence by outcome for HBOT as a treatment for cerebral palsy

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Motor function	Mixed (1 showed no benefit, 2 showed benefit)	3 fair	Low
Caregiver/Pediatric Evaluation of Disability Inventory (PEDI)	Benefit	1 fair, 1 poor	Low
Other disease-specific outcomes	Benefit	2 poor	Very low

HBOT for Multiple Sclerosis

One systematic review, including 9 RCTs (10 publications) (504 participants), reported on the effectiveness of HBOT for the treatment of multiple sclerosis (MS). The primary outcomes evaluated included objective assessments of improvement in MS by a neurologist/hyperbaric physician (Kurtzke Expanded Disability Status Scale [EDSS] and the number of patients suffering disease exacerbations), secondary outcomes included global and individual Functional Status Scores (FSS) assessed by a neurologist, as well as those reported by the patient.

Reduction in EDSS: Moderate-quality evidence from 5 pooled trials (271 participants) (2 good quality, 3 fair) found no significant reduction in disability among MS patients receiving HBOT versus sham treatment immediately posttreatment (mean EDSS change in HBOT group versus sham, –0.07; 95% CI, –0.23 to 0.09), or at 6 months follow-up (mean EDSS change in HBOT group versus sham, –0.22; 95% CI, –0.54 to 0.09). The 6-month results were based on pooled data from 3 trials. Two trials (81 participants) were pooled to examine the outcome at 1-year posttreatment and found a significant reduction in mean EDSS in the HBOT group versus the sham treatment group (mean change, –0.85; 95% CI, –1.28 to –0.42). These 2 trials, however, were the only trials to provide positive data among 9 included studies.

Prevention of exacerbation: Moderate-quality evidence from 5 studies (1 good quality, 4 fair quality) suggests that HBOT does not significantly reduce the chance of having an exacerbation at 1 month (odds ratio [OR], 0.31; 95% CI, 0.01-7.8), 6 months (OR, 0.74; 95% CI, 0.25-2.22,) or 12 months (OR, 0.38; 95% CI, 0.04-3.22; *P*=0.4) following treatment.

FSS: Moderate-quality evidence from 4 pooled studies suggests that HBOT does not improve functioning among MS patients. Four studies were pooled to determine if HBOT improved global FSS scores at the end of 20 treatment sessions. The results showed no significant difference between groups in overall FSS (29% improvement in the HBOT group versus 28% in the sham group) (OR, 1.17; 95% CI, 0.59-2.33). Similarly, 7 of the 9 included trials reported no significant difference between HBOT and sham treatment in terms of individual FSS elements. Two studies showed improved pyramidal function at 6 and 12 months follow-up.

Quality assessment and summary: Moderate-quality evidence from 9 trials suggests little effect of HBOT on outcomes related to MS. Two small, good-quality trials found modest benefits, while 7 fair-quality trials found no benefit. Furthermore, the statistical benefits observed in the 2 positive trials are unlikely to translate into clinically significant benefits for the patient. Of note, there were no RCTs found on this topic post 1990, and there appears to be little interest in further investigation into the use of HBOT for MS.

Summary of evidence by outcome for HBOT as a treatment for multiple sclerosis

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Reduction in Expanded Disability Status Scale (EDSS)	0 and 6 months f/u (n=7 studies): No benefit 12 month f/u (n=2 studies): Benefit	2 good, 3 fair	Moderate
Prevention of exacerbation	No benefit	1 good, 4 fair	Moderate
Functional Status Score (FSS)	Global FS: No benefit Individual FSS: No benefit Pyramidal FS: Benefit	2 good, 7 fair	Moderate

HBOT for Migraines and Cluster Headaches

One good-quality systematic review (119 participants), including 7 RCTs, reported on the effectiveness of HBOT for the treatment and prevention of cluster headaches or migraines. The outcomes evaluated included relief from migraine/headache, requirement for rescue medication; pain intensity; number of headache days per week; sustained relief; and headache index.

Migraines: Moderate-quality evidence from 3 pooled fair-quality trials (43 participants) found a significant relief from acute migraines following 40 to 45 minutes of HBOT. The results suggest that more than 70% of sufferers will obtain relief with an NNT of 2 (95% CI, 1-2) compared with a sham treatment. There is very-low-quality evidence for all other outcomes. For example, a fair-quality trial (40 participants) found no significant difference in the percentage of patients requiring rescue medication in the first week after receiving HBOT versus a sham treatment (RR, 0.84; 95% CI, 0.64-1.11), no difference in the percentage of patients experiencing nausea with or without vomiting (RR, 1.27; 95% CI, 0.68-2.38), and no differences between groups in the mean number of headache days per week during 1, 4, or 8 weeks posttreatment (MD during week 1, –0.13; 95% CI, –1.41 to 1.15; MD during week 4, –0.25; 95% CI, –1.52 to 1.02; MD during week 8, –0.75; 95% CI, –2.06 to 0.56). Similarly, another trial reported no difference between groups in mean pain intensity score immediately posttreatment among 8 patients enrolled in a crossover trial (MD, 2.8; 95% CI, –4.69 to 10.29).

Cluster headaches: The evidence related to the use of HBOT for cluster headaches is of very low quality. One small, poor-quality trial (13 participants) found that more patients experienced relief from cluster headaches within 20 minutes of receiving HBOT (6 of 7 patients) than those that did not receive HBOT (0 of 6) but the result was not significant (RR, 11.38; 95% CI, 0.77-167.85). The study found that 86% of the HBOT group obtained relief and sustained it for 48 hours versus none in the sham group, but the study did not have the power to find the effect significant. Another small crossover trial of fair quality involving 16 patients found that HBOT offered no benefit in the treatment of cluster headaches over controls (RR, 0.98; 95% CI, 0.40-2.41).

Quality assessment and summary: Moderate-quality evidence from 3 fair-quality RCTs suggest that 40 to 45 minutes of HBOT is effective in significantly relieving an acute migraine attack. Just 2 patients need to be treated to obtain significant relief for 1 additional patient. There is no evidence that HBOT can prevent migraines, reduce the nausea and vomiting associated with migraines, or reduces the need for rescue medication. There is insufficient evidence from 2 studies to determine the effectiveness of HBOT for preventing, relieving, or terminating cluster headaches.

Summary of evidence by outcome for HBOT as a treatment or prevention for migraines and cluster headaches

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Migraine relief	Benefit	3 fair	Moderate
Reduction in nausea and vomiting	No benefit	1 fair	Very low
Need for rescue medication	No benefit	1 fair	Very low
Migraine pain intensity	No benefit	1 fair	Very low
Frequency of migraines	No benefit	1 fair	Very low
Relief from cluster headaches	No benefit	1 poor	Very low
Headache index	No benefit	1 fair	Very low

HBOT for Sensorineural Hearing Loss

One good-quality systematic review from the Cochrane Collaboration, originally published in 2007 (including 7 RCTs, 396 participants), plus 1 fair-quality RCT (57 participants), published subsequently, reported on the effectiveness of HBOT as a treatment for sensorineural hearing loss. Studies can be divided into those that looked at HBOT in the acute or chronic phases following the onset of hearing loss. The primary outcome across studies was improvement or return of hearing.

Acute phase: There is some low-quality evidence for the use of HBOT as a treatment for sensorineural hearing loss in the acute phase (within 2 weeks) of the disease (4 fair quality, 4 poor quality). Pooled data from 2 trials (114 participants) (1 fair quality, 1 poor quality) found a significant improvement in the proportion of patients with > 25% return of hearing at the end of HBOT versus control (RR, 1.39; 95% CI, 1.05-1.84; NNT, 5; 95% CI, 3-20) but no significant improvement in the proportion of patients with > 50% return of hearing (RR, 1.53; 95% CI, 0.85-2.78). A fair-quality trial (50 participants) found that patients receiving HBOT had a significantly better improvement in pure-tone average (PTA) from baseline to posttreatment than did controls (weighted MD, 37% in favor of HBOT; 95% CI, 22%-53%), and pooled data from 2 studies (1 fair quality, one poor quality) found a significant mean improvement in hearing over all frequencies among the HBOT group versus controls (MD, 15 dB greater with HBOT; 95% CI, 1.5-29.8). In contrast, 1 fair-quality trial (20 participants) found no significant difference between groups in the absolute improvement in PTA > 20 dB (RR for absolute improvement with HBOT, 3.0; 95% CI, 0.14-65.9), and a fair-quality RCT involving 57 patients (published subsequent to the Cochrane Review) found no significant benefit to HBOT in addition to steroids versus steroids alone (79% complete or moderate recovery among the HBOT group versus 71% among the control group; *P*=NS).

Chronic phase: Moderate-quality evidence from 2 fair-quality trials suggests no benefit to HBOT in the chronic phase of sensorineural hearing loss. One trial reported no significant difference between groups in the proportion of patients with improvement in PTA (RR for improvement with HBOT, 0.64; 95% CI, 0.30-1.33), and another found no significant mean improvement in hearing across all frequencies (MD, 1.4 dB in favor of HBOT group; 95% CI, –3.2 to 6.0).

Quality assessment and summary: Low-quality evidence (due to mixed results) from 8 RCTs is inconclusive as to whether there is a benefit of HBOT for the treatment of sensorineural hearing loss in the acute phase. A large systematic review suggests that HBOT is beneficial among patients who present within 2 weeks of onset of the disease; however, there is no evidence that the statistical benefit observed translates into a functional benefit, and the results from a recent RCT do not support that finding. Moderate-quality evidence suggests that HBOT provides no added benefit to patients presenting with chronic sensorineural hearing loss.

Summary of evidence by outcome for HBOT as a treatment for sensorineural hearing loss

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Hearing improvement/recovery in acute sensorineural hearing loss	Mixed	4 poor, 4 fair	Low
Hearing improvement/recovery in chronic sensorineural hearing loss	No benefit	2 fair	Moderate

Findings, Key Question #1a: What is the optimal frequency, dose, and duration of HBOT treatment?

Several systematic reviews planned to examine the optimal frequency, duration, and dose of treatment for HBOT but found very little data in the published research. Three systematic reviews conducted some form of subgroup analyses relevant to the question of frequency and dose but none looked at the duration of treatment sessions.

Frequency of HBOT Sessions

Low-quality evidence from 8 studies (3 good, 1 fair, 4 poor quality) provided mixed results on the optimal frequency for HBOT. A 2012 systematic review pooled data from 5 RCTs and found no significant benefit of HBOT for major amputation rate among patients with diabetic foot ulcers for either a short course of HBOT (< 30 treatment sessions) (RR, 0.29; *P*=0.08) or a longer course (> 30 sessions) (RR, 0.40; *P*=0.29). A 2011 systematic review examining the effects of HBOT on MS found conflicting results from 2 good-quality trials that looked at number of treatment sessions. One trial found that there was a significant benefit of HBOT for those having a shorter course of treatment (20 session versus 20 sessions plus 5 months of boosters) (shorter course mean change in HBOT group versus sham, –0.84; 95% CI, –1.43 to –0.25; longer course mean change in HBOT group versus sham, –0.29; 95% CI, –0.91 to 0.33). However, the other trial found a significant benefit of HBOT for those having a longer course of treatment but not for the shorter course (20 session versus > 20 sessions) (longer course: OR, 0.19; 95% CI, 0.05-0.73; shorter course: OR, 0.34; 95% CI, 0.01-8.64). The heterogeneity between the trials could not be explained by looking at dose or differences in the control groups. In addition, a poor-quality case series of 19 patients found no differences in hearing improvement based on number of treatment sessions (> 30 sessions versus < 30 sessions) or if treatment was provided within 15 days of presentation versus between 15 and 30 days.

Dose

Low-quality evidence from 5 trials (4 fair quality, 1 poor quality) was insufficient to determine the optimal dose for HBOT. Data from 4 pooled trials (3 fair quality, 1 poor quality) found that the application of high treatment pressure (2 ATA), among patients with TBI was associated with a better outcome than lower treatment pressure (1.5 ATA) (unfavorable functional outcome at 2.5 ATA: RR, 0.48; 95% CI, 0.27-0.87; unfavorable outcome at 1.5 ATA: RR, 0.47; 95% CI, 0.08-2.85; *P*=0.41). However, there was significant heterogeneity between the included studies. Conversely, one fair-quality trial found that HBOT was more effective than air in relieving acute migraines (RR, 6.23; 95% CI, 0.47-82.92) but no better than normobaric oxygen (RR, 9.0; 95% CI, 1.39-58.44).

Summary and Quality Assessment

The available data from 13 studies provides insufficient evidence to determine the optimal treatment frequency duration or dose for HBOT. No studies reported on the optimal duration of treatment sessions; there were mixed results from subgroup analysis involving 8 studies looking at frequency; and significant heterogeneity means that we have low confidence in the available results from 5 studies that looked at dose.

Summary of the evidence related to the frequency, duration, or dose of HBOT

	Frequency of HBOT Sessions	Duration of Treatment Sessions	Dose
Range across studies	1-101	20-120 minutes	1.0-3.0 ATA
Findings from subgroup analyses	No difference between a longer treatment course (>30 sessions) and a shorter course (<30 sessions) among patients with diabetic foot ulcers or sensorineural hearing loss; conflicting results for patients with multiple sclerosis	None	Oxygen dose of 2.5 atmospheres absolute (ATA) was more effective than 1.5 ATA for patients with traumatic brain injury (TBI) but the heterogeneity between studies was very high
Optimal	Unable to determine	Unable to determine	Unable to determine
Overall quality of individual studies	Fair	NA	Fair
Quality of the body of evidence	Low	NA	Low

Findings, Key Question #2: What harms are associated with HBOT?

Fifteen systematic reviews provided data on the safety of HBOT for the indications under investigation. We also included data from 4 primary data studies obtained through a search of the literature for harms-specific studies as well as harms data from 4 related Hayes HTA reports.

The overall evidence suggests that harms associated with HBOT are generally mild and self-limiting. The majority of reported harms include barotrauma, temporary visual disturbances, and, more rarely, oxygen toxicity. Occasional reports of seizures represent the most serious side effects. The Medical Services Advisory Committee (MSAC) of Australia reported an overall harms incidence rate of 6.3%; 17% incidence of general pain or discomfort during decompression; 4.8% incidence of ear pain; 1.5% incidence of tympanostomy tube placements; 0.9% incidence of persistent ocular changes; 0.6% incidence of ear barotrauma; 0.34% incidence of abdominal pain; and 0.1% incidence of claustrophobia.

Notable indication-specific harms found in the literature include the following:

- Among patients with LRTI, there were reports of ear pain (16% in a trial of 150 patients), transient myopia (3% in one study 8% in another), and confinement anxiety (1.7%).
- Pooled data from 2 trials reported severe pulmonary complications among 13% of TBI patients receiving HBOT compared with none in the control groups (RR, 15.57; 95% CI, 2.11-114.72).
- One study reported ear problems among 47% of children with cerebral palsy receiving HBOT versus 22% among controls (*P* significant but value not reported). Another study reported a 12% seizure rate and found that 35% of patients reported ear problems. Another reported that 8% of 50 children stopped treatment due to adverse events, including seizures, and one other study reported 1 seizure in an observational study of 230 patients.
- Among patients with MS, a 2011 Cochrane Collaboration review reported 77 patients (55%), across 4 trials, suffered temporary deterioration in visual acuity in the HBOT group versus 3 patients (2.3%) in the sham group (OR, 24.87; 95% CI, 1.44-428.5; NNT, 1; 95% CI, 1-2).

Summary and Quality Assessment

Few studies report harms as a primary outcome and many of the most revealing studies on harms come from poor-quality observational studies. We did not rate the quality of each individual study reporting harms but the evidence is consistent and generalizable. We suggest that there is moderate evidence from across 15 systematic reviews, 4 additional primary data studies and 4 Hayes Medical Technology Directory reports that the harms associated with HBOT are usually mild, self-limiting with most resolving after termination of treatment. The most common harms include myopia, barotrauma, claustrophobia, and oxygen toxicity. Life-threatening adverse events are rare but do occur on occasion and can include seizures and death. There is insufficient evidence to comment on specific risks for subpopulations.

Findings, Key Question #3: What is the differential effectiveness and safety of HBOT according to factors such as age, sex, race or ethnicity, disability, comorbidities, wound or injury duration and severity, and treatment setting?

A number of systematic reviews planned subgroup analysis a priori but were unable to carry out analyses due to a lack of data. Of 21 included systematic reviews in this report, 6 provide evidence relevant to KQ3. In addition, 4 primary data studies (2 RCTs, 1 pre-post study, and 1 cases series), not included in the selected reviews, report on differential effectiveness.

We found no relevant data on the differential effectiveness and safety of HBOT according to sex, race, ethnicity, disability, wound duration, or treatment setting. The following indication-specific evidence was found in relation to age, radiation exposure, and disease severity:

- Low-quality evidence from 2 studies (1 fair-quality RCT, 1 poor-quality case series) suggests that among patients with sensorineural hearing loss, there is no significant difference in hearing recovery among patients < 50 years of age compared with those ≥ 50 years of age (P>0.05).
- Very-low-quality evidence from 1 fair-quality trial (60 TBI patients) found that younger TBI patients (< 30 years of age) were more likely to recover consciousness by 1 month following HBOT compared with controls (6 of 9 versus 1 of 9; P<0.03).
- Among patients with sensorineural hearing loss, mixed results from 3 RCTS (1 fair quality, 2 poor quality) was insufficient to determine if HBOT was more or less effective according to the degree of hearing loss severity. Pooled data from 2 RCTs (1 fair quality, 1 poor quality) found a significant improvement in mean hearing with HBOT among those with severe hearing loss (n=14) at enrollment (MD, 37.7 dB; 95% CI, 22.9-52.5) but not among those with mild hearing loss (n=19) at enrollment (MD, 0.2; 95% CI, –10 to 10.4). In contrast, a poor-quality trial found that severity of hearing loss was not related to either a 25% or 50% improvement in hearing following HBOT.
- Low-quality evidence from 9 included studies (1 RCT, 8 observational) found that ORN following post-irradiation extraction was more likely among head and neck cancer patients having received a radiation dose > 60 grays (Gy) versus those who received lower radiation doses (< 60 Gy), suggesting that HBOT may be more effective among patients exposed to > 60 Gy of radiation therapy.
- Low-quality evidence from 1 fair-quality RCT and 4 poor-quality uncontrolled observational studies suggest that transcutaneous oxygen measurement for nonhealing wounds (i.e., elevated oxygen breathed under normobaric conditions outside of a hyperbaric chamber) can determine which patients are most likely to benefit from HBOT.

In addition, data from a nonsystematic review included in a 2008 Hayes HTA reported untreated pneumothorax as the only absolute contraindication to HBOT. Lung disease, previous ear surgery or trauma, significant upper respiratory infections, fever, and claustrophobia are considered relative contraindications, depending on their severity. In addition, preexisting cataracts, optic neuritis, and pregnancy are thought to be relative contraindications. Certain medications, including steroids, amphetamines, catecholamines, insulin, and thyroid hormone, may enhance central nervous system oxygen toxicity, and patients who are receiving these and other medications should be monitored closely during HBOT. A small, poor-quality pre-post test investigating the influences of HBOT on blood pressure (BP), heart rate, and blood glucose among 41 patients with a variety of indications found that underlying diseases and concomitant medical treatments significantly influence the effects of HBOT on vital signs. Overall, mean systolic and diastolic BP were significantly higher post HBOT (MD, 7 millimeters of mercury [mm Hg]; *P*=0.001; and MD, 8.9 mm Hg; *P*<0.001, respectively). Heart rate decreased by 18% (*P*<0.001), and blood sugar levels dropped from 231 milligrams per deciliter (mg/dL) (SD, 95) pretreatment to 170 mg/dL (SD, 85.8) posttreatment (*P*<0.001). The authors found that patients with diabetes and hypertension suffered higher elevations in systolic BP and a greater drop in heart rate than did comparison groups.

Summary and Quality Assessment

There is no evidence to determine the differential effectiveness and safety of HBOT according to sex, race, ethnicity, disability, wound duration, or treatment setting. There is evidence of very low quality suggesting that younger TBI patients may recover faster with HBOT than older patients. There is low-quality evidence suggesting that radiation dose influences the effectiveness of HBOT to prevent ORN among head and neck cancer survivors. There is also low-quality evidence that TCOM may predict those most likely to benefit from HBOT. There is insufficient evidence from poor-quality studies to determine the differential safety of HBOT across populations.

Findings, Key Question #4. **What are the cost implications of HBOT, including the cost-effectiveness, compared to alternative treatments?**

Cost estimates on the provision of HBOT are sparse. A 2006 UK-based cost analysis estimated capital start-up costs between GBP 64,800 to 72,000 (USD 104,985 to 116,650) (conversion to USD using rate on September 20, 2012), and cost per treatment ranging from GBP 32 to 41 (USD 52 to 66). Older data from the U.S. reported costs in 1996 of between USD 300 to 400 for an average 90-minute session. The average total allowed charge per treatment in the U.S. in 1998 was USD 405, with an average allowed therapy cost per patient of approximately USD 12,000.

Two good-quality systematic reviews were selected to answer KQ4. Together, they include 11 studies and provide low-quality evidence on the cost-effectiveness of HBOT for diabetic wounds, nondiabetic nonhealing wounds, ORN, and thermal burns.

Cost-Effectiveness of HBOT for Diabetic Wounds

Five studies investigating the cost-effectiveness of HBOT for the treatment of diabetic wounds suggested that HBOT was cost effective under the assumptions of the various models, but only one model was robust during sensitivity analysis, suggesting that cost-effectiveness varies widely depending on the various cost and effectiveness parameters employed. A 2007 Canadian-based decision tree

analysis suggested that adjunctive HBOT was dominant over standard care alone, with 3.64 quality-adjusted life-years (QALYs) gained among the HBOT group versus 3.01 among controls. The 12-year cost to the patient was CAD 40,695 (USD 41,625) for the HBOT group and CAD 49,786 (USD 50,924) for controls (costs were in 2004 Canadian dollars). The results remained stable in a sensitivity analysis, suggesting that the model was robust and reliable.

Cost-Effectiveness of HBOT for Nondiabetic Nonhealing Wounds

A 2003 report from the Medical Services Advisory Committee (MSAC) of Australia suggested that among patients with nondiabetic nonhealing wounds, the treatment costs for a one third reduction in wound size with HBOT were AUD 6941 (USD 7233) per patient per 30 HBOT sessions (conversion to USD using rate on September 20, 2012). The cost-effectiveness (we assume a payer perspective) to cure 1 person of a chronic leg ulcer was AUD 27,764 (USD 28,933). However, the model was sensitive to the assumptions and therefore we have low confidence in the estimates provided.

Cost-Effectiveness of HBOT for ORN

Three studies investigating the cost-effectiveness of HBOT for the treatment of ORN suggested that HBOT was cost effective but all were sensitive to the assumptions of the models. A 1997 cost-effectiveness analysis on the use of HBOT for ORN of the mandible found HBOT to be dominant over the hypothetical control estimating cost savings of CAD 53,147 (USD 54,362) (conversion to USD using rate on September 20, 2012). A 2000 Australian report estimated an incremental cost-effectiveness ratio (ICER) of AUD 28,480 (USD 29,680) to avoid one case of ORN with the addition of HBOT. Also in 2000, a UK-based analysis on the use of HBOT to treat ORN following dental extraction in an irradiated field found the estimated cost per patient per year using HBOT to be GBP 20,000 (USD 32,403) versus GBP 5000 (USD 8101) among non-HBOT controls. Sensitivity analysis suggested that the break-even costs of treating ORN ranged from GBP 17,500 to 127,500 (USD 28,352-206,568) (conversion to USD using rate on September 20, 2012).

Cost-Effectiveness of HBOT for Burns

A poor-quality 1990 U.S. study comparing HBOT plus standard wound care with standard wound care alone among 21 patients with 19% to 50% total body surface area burns found that the HBOT group had an average decrease in the length of hospital stay of 14.8 days compared with controls, a reduction in surgical procedures of 39% and an average saving per case of $31,600. This result conflicts with the efficacy data reported earlier, suggesting that there is insufficient evidence to support the use of HBOT for the treatment of burns.

Summary and Quality Assessment

HBOT may be cost effective under very specific assumptions of effectiveness and costs. All included cost analyses found HBOT to be cost effective or cost saving. However, the available economic evaluations were severely limited by sparse cost data and unreliable efficacy and cost estimates used to make model assumptions. Only one model was found to be robust during sensitivity analysis, making most estimates very unreliable. Overall, there is low-quality evidence to suggest that HBOT may be a cost effective treatment under certain conditions, for certain populations and indications.

Practice Guidelines

We did not find guidelines on the use of HBOT for the treatment of MS, headaches and migraines, or brain injury. Refractory osteomyelitis was not the focus of any review but was mentioned in at least one included guideline. In all, we included 14 generally good-quality guidelines. Two were cross-cutting in nature covering multiple indications; 2 were specific to the use of HBOT for the management of diabetic foot ulcers; 4 provided guidelines on the use of HBOT for pressure ulcers; 1 on the management of lower extremity amputations; 1 on nonhealing ischemic wounds; 1 on ORN; 1 on cerebral palsy; 1 on sensorineural hearing loss; and 1 systematic review, which provided guidelines for the use of HBOT among critically ill intubated, mechanically ventilated patients.

- Cross-cutting: Two guidelines (1 good quality, 1 fair quality) were consistent with the evidence recommending HBOT only in cases of nonhealing wounds where standard care has not worked and recognizing that the level of evidence pertaining to diabetic wounds is stronger than the evidence for other nonhealing wounds.
- Diabetic nonhealing wounds: The Wound Healing Society in the U.S. recommended considering HBOT for diabetic foot ulcers based on moderate evidence (fair quality). In contrast, despite the guidelines recognition of moderate-level evidence for the use of HBOT for diabetic foot ulcers, National Institute for Health and Clinical Excellence (NICE) in the UK recommended against the use of HBOT for inpatients with diabetic foot ulcers unless as part of a clinical trial in a good-quality guideline.
- Other nonhealing wounds: Consistent with the evidence, 3 of 4 guidelines (3 good quality, 1 fair quality) recommended against the use of HBOT as adjunct treatment in the management of pressure ulcers because of insufficient evidence. Despite the lack of supporting evidence, the Registered Nurses' Association of Ontario recommended that HBOT be considered for the management of pressure ulcers basing their recommendation on expert opinion and consensus. Fair-quality guidelines on the management of lower extremity amputations from the Veterans Administration (VA) and Department of Defense (DOD) are consistent with the evidence, whereas the Wound, Ostomy and Continence Nurses Society (2008**)** recommended that HBOT be considered for lower extremity arterial ulcers for which there is little evidence (fair quality).
- LRTI: The Dutch Head and Neck Oncology Cooperative Group (2007) recommended HBOT for the treatment of ORN of the mandible (fair quality).
- Cerebral palsy: Also consistent with the evidence, the Canadian agency AETMIS recommended against the use of HBOT for cerebral palsy (fair quality)
- Sensorineural hearing loss: The most recent good-quality guideline was a 2012 guideline from the American Academy of Otolaryngology – Head and Neck Surgery recommending the use of HBOT for the treatment of sensorineural hearing loss among patients presenting within 2 months of onset. The panel felt that the level of evidence for hearing improvement, albeit modest and imprecise, was sufficient to promote greater awareness of HBOT as an intervention for SSHL.
- Critically ill patients: One systematic review examining the use of HBOT for critically ill intubated, mechanically ventilated patients provided guidelines on the safe use of the technology for that population and for the personnel involved (poor quality).

Selected Payer Policies

Reimbursement policies among the four agencies examined (CMS, Aetna, Regence BCBS, and Group Health) reflect the findings of this report. Conditions that have at least moderate-quality evidence supporting the efficacy and safety of HBOT are covered by most, if not all, agencies. Conditions with moderate-quality evidence showing no benefit of HBOT are not covered, and agencies are split over those conditions where the evidence conflicts, is weak, or insufficient. For example, all of the agencies cover the use of HBOT for the management of diabetic nonhealing wounds, including foot ulcers (using similar definitions for the category of nonhealing wound), refractory osteomyelitis, ORN, and soft tissue radionecrosis. Three of four also cover crush injuries, compromised skin grafts, and peripheral arterial insufficiency. None offer coverage for HBOT as a treatment for headaches/migraine, thermal burns, brain injury, cerebral palsy, or MS. One group (Aetna) offers coverage for sensorineural hearing loss; one does not cover compromised skin grafts (Regence BCBS) and one does not cover peripheral arterial insufficiency (Regence BCBS).

Overall Summary and Discussion

There have been several good-quality systematic reviews published in the last 10 years, some of which provide moderate-quality evidence of the effectiveness and harms associated with HBOT. However, the current evidence remains insufficient to definitively answer questions of effectiveness in relation to a number of indications. Furthermore, there is little evidence on the optimal frequency, duration, and dose of treatment and little known about which subpopulations are likely to benefit most from treatment.

Indications for Which There Is Moderate-Quality Evidence of the Effectiveness of HBOT

Moderate-quality evidence supports the addition of HBOT to standard wound care to promote short-term wound healing and limb salvage among patients with diabetic foot ulcers. There is no evidence of improvement beyond 1 year and there is insufficient evidence to determine the effect of HBOT on QOL or other health outcomes. There is also moderate-quality evidence suggesting that HBOT improves outcomes of LRTI affecting bone and soft tissues. There is no overall estimate of effect because of the heterogeneity between studies, but the evidence suggests that radiation-induced tissue and bone damage to the head and neck, anus, and rectum may benefit from HBOT. In addition, there is moderate-quality evidence that HBOT reduces the risk of developing ORN following tooth extraction in a previously irradiated area. Moderate-quality evidence also suggests that HBOT reduces the risk of dying following TBI but does not improve functional outcomes. Finally, moderate-quality evidence suggests that 40- to 45-minutes of HBOT is effective in significantly relieving an acute migraine attack but there is no evidence that HBOT can prevent migraines, reduce the nausea and vomiting associated with migraines, or reduces the need for rescue medication.

Indications for Which There Is Low-Quality Evidence of the Effectiveness of HBOT

There is limited low-quality evidence suggesting that HBOT may improve healing when employed as an adjunct treatment for venous ulcers, flaps and grafts, crush injuries, and surgical reconstruction (without grafts or flaps) but more study is needed to support the current evidence. Low-quality evidence (due to mixed results) is inconclusive as to whether or not there is a benefit of HBOT for the treatment of sensorineural hearing loss in the acute phase of the disease. A large systematic review suggests that HBOT is beneficial among patients who present within 2 weeks of onset; however, there is no evidence

that the statistical benefit observed translates into a functional benefit, and the results from a recent RCT do not support that finding. Of note, HBOT as an adjunct treatment for refractory osteomyelitis is only supported by low-quality evidence (primarily because of poor study design), 1 small fair-quality nonrandomized trial suggests that HBOT may reduce the rates of relapse infection among patients with refractory osteomyelitis but further good-quality studies are necessary to confirm this finding. In addition, there is also low-quality evidence suggesting that transcutaneous oxygen measurement (TCOM) can identify patients most likely to benefit from HBOT, as well as low-quality evidence suggesting that patients having received a radiation dose > 60 Gy for the treatment of head and neck cancer and requiring extraction of mandibular teeth within the radiated field may benefit from HBOT.

Indications for Which There Is Moderate-Quality Evidence of No Effectiveness of HBOT

Moderate-quality evidence suggests little benefit of HBOT for the treatment of MS. Of note, is that there were no RCTs found on this topic post 1990 and there appears to be little interest in further investigation into the use of HBOT for multiple MS.

Indications for Which There Is Low-Quality Evidence of No Effectiveness of HBOT

Low-quality evidence suggests no benefit of HBOT for preventing, relieving, or terminating cluster headaches. There is also no evidence that HBOT is beneficial among patients presenting with chronic sensorineural hearing loss.

Indications for Which There Is Insufficient Evidence to Assess Effectiveness

There is insufficient evidence, primarily due to mixed results or an overall paucity of studies, to determine if HBOT is effective for the treatment of thermal burns, cerebral palsy, or brain injuries other than TBI.

Cost-Effectiveness

The available cost analyses are limited by sparse cost data and a wide range of efficacy estimates. Under the base case model assumptions employed in the included cost analyses, there is a low quality of evidence to suggest that HBOT may be cost effective or cost saving for the treatment of diabetic nonhealing wounds and the prevention of ORN. The base case assumptions and sensitivity parameters used as estimates for HBOT effectiveness were in line with the estimates found in this report and found to be of moderate quality. The results demonstrated cost-effectiveness under base case assumption but proved not to be robust when a range of parameters were examined during sensitivity analyses. Cost analyses for the use of HBOT for nondiabetic nonhealing wounds and burns, also found HBOT to be cost effective under base case assumption but once again were very sensitive to the range of effectiveness parameters employed during sensitivity analyses, suggesting the models were not robust and therefore unreliable. In addition, we found the evidence supporting the use of HBOT for nondiabetic nonhealing wounds and burns to be of low and insufficient quality, respectively, indicating the need for further caution in interpreting the cost analyses for these indications. Overall, there is a low quality of evidence to suggest that HBOT may be a cost-effective treatment under certain conditions and for certain populations and indications, but current data are insufficient to determine the most cost-effective uses of the technology.

Harms

There is moderate-quality evidence from across studies that harms associated with HBOT are usually mild, self-limiting, and with most resolving after the termination of treatment. The most common harms include myopia, barotrauma, claustrophobia, and oxygen toxicity. Life-threatening adverse events are rare but do occur on occasion and can include seizures and death. There is some evidence but of unknown quality that comorbidities such as lung disease, previous ear surgery or trauma, significant upper respiratory infections, fever, claustrophobia, preexisting cataracts, optic neuritis, and pregnancy are contraindications for HBOT.

Key Gaps in the Evidence

- Future work needs to focus on designing methodologically rigorous studies, adequately powered, free from the risk of publication bias and generalizable to the population of patients under review.

- To determine definitive patient selection criteria, future studies need to specifically address the question of frequency, duration, and dose of treatment as well as the question of differential effectiveness across each indication and for a variety of subpopulations.

- Robust models arising from more reliable cost and effectiveness data are necessary to determine the true cost-effectiveness of HBOT for the various indications.

BACKGROUND

Hyperbaric oxygen therapy (HBOT) involves the systemic administration of 100% oxygen inside a treatment chamber under pressures greater than 1 atmosphere absolute (ATA). The potential benefits of HBOT arise from a combination of increased hydrostatic pressure and tissue oxygen tension. In the hyperbaric oxygen (HBO) chamber, the elevated concentration and pressure of oxygen increase the plasma oxygen concentration by 10 to 15 times, increasing oxygen delivery to the tissues. In single-patient HBO chambers, all of the air is replaced with pure oxygen gas, and direct diffusion of oxygen into open wounds may enhance tissue oxygenation. HBO may also be administered in a multiplace chamber in which patients breathe 100% oxygen through a facemask or similar device with the surrounding air pressure increased to 2 to 3 times the atmospheric pressure. In either case, hyperoxygenation directly supports tissues that are poorly perfused due to compromised blood flow. Although the hyperoxygenation is temporary, tissue viability may be sustained, enhancing the efficacy of other therapies or enabling a new blood supply to be established. In addition, intermittent hyperoxia may promote osteogenesis, normal fibroblast proliferation, epithelialization, and collagen synthesis in areas of compromised blood flow. Another apparent benefit of HBOT is that it causes peripheral vasoconstriction through arteriolar smooth muscle stimulation (Schaefer, 1992; Roth and Weiss, 1994; Tomaszewski and Thom, 1994; Uzun et al., 2008).

HBOT has been available for several decades and has been advocated as a treatment for many indications over the years. At one point in the late 1960s to early 1970s, HBOT was being used to treat as many as 28 conditions for which there was very little evidence (De Laet et al., 2008). In more recent years, there has been increased scrutiny into the efficacy and safety of HBOT for a wide variety of conditions with new evidence often emerging. It remains unclear as to the indications for which HBOT is most effective and safe. Among the indications for which questions still remain are diabetic nonhealing wounds, including foot ulcers; other nonhealing wounds, including skin and tissue grafts, thermal burns, and surgical wounds; refractory osteomyelitis; late radiation tissue injury (LRTI); brain injury; cerebral palsy; headache/migraine; multiple sclerosis; and sensorineural hearing loss.

Potential Indications for HBOT

Diabetic Wounds

Foot wounds are one of the most common complications of diabetes and are responsible for substantial morbidity and mortality. Diabetes mellitus affects approximately 23.6 million individuals in the United States, or 8% of the adult population (ADA, 2011). It is estimated that 50% of all nontraumatic lower extremity amputations performed in the United States are due to diabetes, with an annual incidence ranging from 37 to 137 per 10,000 patients. At any given time, lower extremity ulcers affect approximately 1 million diabetics. These lesions often develop due to sensorimotor and autonomic neuropathies and associated lack of sensation within the diabetic foot that lead to alterations in pressure distribution, foot deformities, and ulceration. In patients with mild lesions uncomplicated by ischemia, conservative treatments such as topical antibiotics, sterile dressings, and unweighting may be sufficient. More severe lesions develop when focal hypoxia in the ankle, foot, or toes occurs as a result of increased blood viscosity, increased platelet aggregation, and capillary obstruction. In diabetic patients, local tissue stresses tend to result in thrombosis and necrosis rather than the more benign inflammatory response that occurs in nondiabetic patients. Once a diabetic foot wound has become chronic, it may be complicated by gas gangrene, which occurs as a result of wound infection by bacterial

species such as *Clostridium perfringens*. Under anaerobic conditions, *C. perfringens* produces toxins that cause tissue necrosis, hemolysis, ischemia, vasoconstriction, and increased vascular permeability. For the diabetic foot wound, HBOT is used along with traditional systemic and topical therapies to promote wound healing. It is purported to antagonize anaerobic infection, improve blood supply, and reduce ischemic nerve damage (Doctor et al., 1992; Williams, 1997; O'Meara et al., 2000; Kranke et al., 2004).

Other Nonhealing Wounds

A chronic wound may be defined as: "any wound that is failing to heal as anticipated or that has been stuck in any one phase of wound healing for a period of six weeks or more" (Collier, 2003, p. 45).

Chronic and Surgical Wounds: Chronic wounds other than those related to diabetes include those with causes that are related to venous insufficiency, pressure, trauma, other vascular disease, and immobilization. Although the causes for chronic wounds vary, in all cases, at least one of the phases of wound healing is compromised (Mustoe, 2004). Surgical wounds present a medical problem if they are large in size, especially if bones and tendons are exposed, and, therefore, are not amenable to primary closure. Proponents of HBOT assert that it provides added benefit to a multidisciplinary approach of debridement, antibiotics, and amputation in patients with demonstrated wound healing deficiencies. HBO-induced hyperoxygenation may restore a favorable cellular environment in which healing and host microbial mechanisms are enhanced. In theory, HBO facilitates collagen release from cells and its subsequent assembly into fibers. In turn, the presence of new collagen fibers creates the proper milieu for the formation of new vasculature. By increasing the oxygen tension in hypoxic wounds, HBOT restores the level of oxygenation required for compromised tissue to function efficiently (Williams, 1997).

Thermal Burns: Approximately 2 million people in the United States suffer burns each year. Thermal burns are the third largest cause of accidental death, with 300,000 serious burns and 6000 fatalities occurring annually. HBO thermal burn therapy is directed at enhancing host defenses, preserving marginally viable tissue, protecting the microvasculature, augmenting neovascularization, and promoting wound closure. Traditional burn care management has similar goals, and incorporates fluid resuscitation, antibiotics, grafting, surgical debridement, and topical ointments. According to some researchers, HBO reduces fluid requirements by approximately 35% in the first 24 hours after a burn, thus minimizing edema. HBOT, used as an adjunct to a comprehensive program of burn care, may also have a direct effect on the pathophysiology of the burn wound (Hart et al., 1974; Kindwall, 1993; Cianci and Sato, 1994).

Skin Grafts and Flaps: HBOT may be beneficial as a means of preparing a base for skin grafts and flaps or preserving compromised grafts and flaps. The goal of postoperative HBOT is the improvement of oxygen delivery to the compromised tissue, with a concomitant improvement in flap and graft viability. Hyperoxygenation provides direct support to tissue that is perfused poorly due to compromised blood flow. HBOT also reduces capillary permeability and edema in compromised tissue. In addition, HBOT may facilitate increased fibroblast migration, collagen synthesis, and capillary angiogenesis, all of which lead to the rapid development of a granulating base and capillary invasion of the graft bed. One further apparent benefit of HBOT is that it reduces white cell adhesion to capillary walls after ischemic or traumatic insult, mitigating the no-reflow phenomenon and increasing red blood cell flexibility. When used in combination with wound dressing, debridement, and antibiotics, HBOT may improve healing in compromised skin grafts and flaps (Bowersox et al., 1986; Kindwall, 1993).

Refractory Osteomyelitis

In the United States, the reported incidence of osteomyelitis is 2 per 10,000 individuals. When bacterial or fungal infection causes pus to form within the bone, the resulting abscesses deprive the bone of its blood supply. Chronic osteomyelitis develops subsequently as ischemia causes bone tissue necrosis. HBOT may prove beneficial when used in conjunction with a standard protocol of parenteral antibiotics, surgical debridement, nutritional support, and reconstructive surgery. The increased oxygen tension experienced during HBOT has a direct antimicrobial effect on anaerobic organisms and some microaerophilic aerobic organisms. An increased oxygen tension also leads to the generation of oxygen radicals, which are lethal or bacteriostatic for anaerobic organisms. Research further suggests that HBO augments the bactericidal action of aminoglycoside antibiotics. In addition, as an adjunct to conventional therapies, HBOT may supply enough oxygen to promote collagen synthesis and angiogenesis in patients with hypoxic osteomyelitic wounds (Leach et al., 1998; Whelan and Kindwall, 1998).

Late Radiation Tissue Injury (LRTI)

More than 1.4 million Americans are diagnosed with cancer each year, and approximately half of these patients receive radiation therapy as part of their management. The side effects of radiation therapy can be very toxic, and radiation oncologists design their treatment protocols to give the optimal dose to control the tumor while minimizing the side effects of radiation exposure. Radiation side effects can be categorized as either acute or delayed (chronic) complications; the latter may develop months or years after radiation treatment and collectively are known as LRTI or late radiation side effects. Late radiation damage is primarily vascular and stromal (connective tissue). The process may progress to the point where normal tissue no longer receives an adequate blood supply, resulting in death or necrosis of the tissue that might necessitate surgical removal. Although any tissue may be affected, LRTI occurs most commonly in the head and neck, chest wall, breast, and pelvis, reflecting the anatomical areas most commonly irradiated. Chronic radiation damage is called osteoradionecrosis (ORN) when bone is damaged and soft tissue radionecrosis when muscle, skin, or internal organs have been damaged. Clinically, ORN presents as exposed irradiated bone that has failed to heal over a period of 3 months (some literature defines it as at least 6 months), unrelated to tumor recurrence. ORN commonly affects the mandible; however, it may also affect other bones, such as the sternum, skull, or pelvis (Gal et al., 2003; Bui et al., 2004; Feldmeier, 2004; Bennett et al., 2005; Teng and Futran, 2005; Wahl, 2006; Esposito et al., 2008; ACS, 2012; UHMS, 2012).

Brain Injury

Traumatic brain injury (TBI) is defined as an injury to the brain by externally inflicted trauma, which may result in significant physical, cognitive, and psychosocial impairment. In the United States, an estimated 1.7 million TBI events occur each year. TBI accounts for more than 1.3 million emergency room visits, approximately 275,000 hospitalizations, and 52,000 deaths annually. The estimated annual direct and indirect cost is approximately $60 billion. (Faul et al., 2010; CDC, 2012). Despite more than 40 years of interest in the use of HBOT for TBI, the evidence of effectiveness has not been convincing (Bennett et al., 2009). Other brain injuries are caused by rapid acceleration or deceleration of the head; nontraumatic bleeding within or around the brain; lack of sufficient oxygen to the brain; or toxic substances passing through the blood-brain barrier. A brain injury results in a temporary or permanent impairment of cognitive, emotional, and/or physical functioning (McDonagh et al., 2003). The use of HBOT for chronic brain injury is based on the theory that, in any brain injury, there are inactive cells that have the potential to recover. According to this theory, these “idling neurons” exist in the ischemic

penumbra, a transition area of dormant neurons between areas of dead tissue and the unaffected healthy tissue. The theory is that oxygen availability to these cells stimulates the cells to function normally, reactivating them metabolically or electrically (McDonagh et al., 2003).

Cerebral Palsy

Cerebral palsy is a neuromuscular disorder that arises in children due to damage of the developing brain. This disorder occurs in 0.1% to 0.5% of live births and is characterized by impairments of muscle control, senses, and perception. Cerebral palsy can develop before, during, or after birth and has many potential causes, including infection, brain hemorrhage, low blood sugar, high levels of bilirubin, drowning, and insufficient blood flow to the brain. Potential symptoms of this disorder include paralysis, weakness, poor coordination, or functional alteration of the motor system, which can result in a number of movement disorders. The specific symptoms vary, depending on the part of the brain that is damaged. There is no known cure for cerebral palsy; the usefulness of HBOT for the treatment of cerebral palsy relates to the possibility of restoring function in portions of the brain that have suffered damage due to lack of oxygenation or other trauma (Hayes, Inc., 2010).

Headache/Migraine

Headache is a common neurological condition characterized by aching or pain that occurs in one or more areas of the head, face, mouth, or neck. The frequency of headaches varies widely from person to person. Headaches may be episodic and occur occasionally or they may be chronic and recur regularly. More than 45 million individuals in the United States suffer from chronic, recurring headaches. Approximately 90% of headaches are primary headaches, which do not arise from an underlying medical condition (NHF, 2012). Cluster headaches are quite rare and occur in only 0.1% of the population; 85% of patients suffering cluster headaches are men. Migraine headache affects more than 28 million individuals in the United States and more than 300 million individuals worldwide (Larson et al., 2011). It has been estimated that 6% of men and 18% of women are affected by migraine headache in the United States (Guyuron et al., 2011; Kung et al., 2011). Many authorities consider both migraine and cluster headaches to be vascular headaches, perhaps related to vascular dilatation. The observation that oxygen administered at higher pressures produced even further vasoconstriction (with preservation of tissue oxygenation) led directly to the suggestion that HBOT might favorably influence vascular headache resistant to conventional drug therapy (Fife et al., 1994).

Multiple Sclerosis

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) that afflicts an estimated 400,000 individuals in the United States and more than 2.5 million worldwide (NMSS, 2012). Although the pathogenesis of MS is not completely understood, it is believed that this disorder involves an autoimmune response mediated by T lymphocytes and autoantibodies that react with myelin proteins (Windhagen et al., 1995). Symptoms associated with MS include fatigue, double or blurred vision, partial or complete vision loss often with optic neuritis, loss of balance and muscle strength, slurred speech, tremors, dizziness, numbness, pain, stiffness, bowel and bladder problems, short-term memory loss, depression, and, in severe cases, partial or complete paralysis. The onset of symptoms usually occurs between the ages of 20 and 50, and women are affected more commonly than men (MSF, 2009; Mayo Clinic, 2010; NMSS, 2012). The use of HBOT as a treatment for MS was originally based on the demonstrated ability of HBOT to produce vasoconstriction with increased oxygen delivery and some anecdotal evidence of efficacy. For several years, there was a flurry of investigation into its effectiveness

for the treatment of MS, which produced a number of randomized studies in the UK, U.S., and Europe (Bennett and Heard, 2011).

Sensorineural Hearing Loss

Sudden sensorineural hearing loss (SSHL), or sudden deafness, is a rapid loss of hearing with onset over a period of > 72 hours. It is associated with ringing in the ears (tinnitus), dizziness, and a feeling of fullness or pressure in the ear. The estimated incidence of SSHL is between 5 and 20 per 100,000 persons per year but may be as high as 300 per 100,000 persons per year. The true incidence of SSHL is likely underestimated, since many who recover quickly never seek medical attention. There are multiple causes of SSHL, which include viral infection, vascular impairment, autoimmune disease, and diseases of the inner ear. The suspected causes of SSHL are unknown in > 70% of cases and a direct causal link for SSHL has not yet been established. HBOT has been proposed for the treatment of SSHL, the rationale being that the hearing loss appears to be caused by a hypoxic event in the cochlear apparatus; therefore, HBOT may potentially reverse the oxygen deficit, increase oxygen pressures in the cochlea, and improve microcirculation. Proving the effectiveness of HBOT for SSHL is complicated given the fact that up to two thirds of SSHL cases resolve spontaneously (Mattox and Simmons, 1977).

Autism

While not under investigation for the current report, there is growing interest in the use of HBOT for the management of autism spectrum disorders. The goal of the therapy is to improve behavioral symptoms of autistic disorder by increasing oxygenation of the brain. Despite the interest, there is a paucity of studies available on the topic, and a 2009 Health Technology Assessment (HTA) by Hayes found insufficient evidence to recommend the use of HBOT for autism (Hayes, Inc., 2009a).

Policy Context

For HBOT, important questions center on the effectiveness of treatment for some conditions, as well as the frequency, dose, and duration of treatment. The list of applications for HBOT has expanded beyond those approved by the Food and Drug Administration (FDA) or currently covered by the Centers for Medicare & Medicaid Services (CMS) and Washington State Health Care Authority (HCA) claims reflected these varied applications.

WASHINGTON STATE AGENCY DATA

Figure 1: Hyperbaric Oxygen (HBO2) Paid Amounts by Agency and Year, 2008-2011

PEB[1]	2008	2009	2010	2011	4 Yr Overall[2]	Average % Change	
Agency Population	204,804	210,501	213,487	212,596		1.3%	
Patient Count	28	34	32	40	118	12.2%	*
Amount Paid	**$308,659**	**$648,082**	**$363,546**	**$609,940**	**$1,930,227**	**42.7%**	*
Per Patient Average Paid	$11,024	$19,061	$11,361	$15,249	$16,358		
Median Paid	$5,771	$15,614	$5,292	$4,449	$5,857		
Maximum Paid	$46,199	$71,141	$52,747	$100,132	$100,132		
Treatments[3]	**575**	**1032**	**822**	**1037**	**3466**	**26.6%**	*
Per Patient Average Treatments	20.5	30.4	25.7	25.9	29.4		
Average Minutes	1,729	1,973	2,477	1,410	2,128		
Medicaid	**2008**	**2009**	**2010**	**2011**	**4 Yr Overall[2]**	**Average % Change**	
Agency Population	392,808	416,817	424,230	435,187		3.5%	
Patient Count	32	35	51	56	156	17.8%	*
Amount Paid	**$212,078**	**$180,452**	**$178,810**	**$244,877**	**$816,217**	**-9.8%**	*
Per Patient Average Paid	$6,627	$5,156	$3,506	$4,373	$5,232		
Median Paid	$3,674	$2,530	$909	$26	$875		
Maximum Paid	$22,480	$28,010	$18,842	$28,072	$28,072		
Treatments[3]	**683**	**631**	**774**	**1,474**	**3,562**	**28.1%**	*
Per Patient Average Treatments	23.6	22.5	17.6	26.8	23.0		
Average Minutes	2,273	1,751	1,183	2,920	2,287		

*Adjusted for population growth

[1] PEB: Public Employee Benefits

[2] 4-year overall patient counts represent unique patients in 4 years. Number of patients may be less than the sum of annual counts.

[3] Each day of treatment for each patient

Figure 2a: PEB Hyperbaric Oxygen (HBO2) Use by Age and Gender, 2008-2011

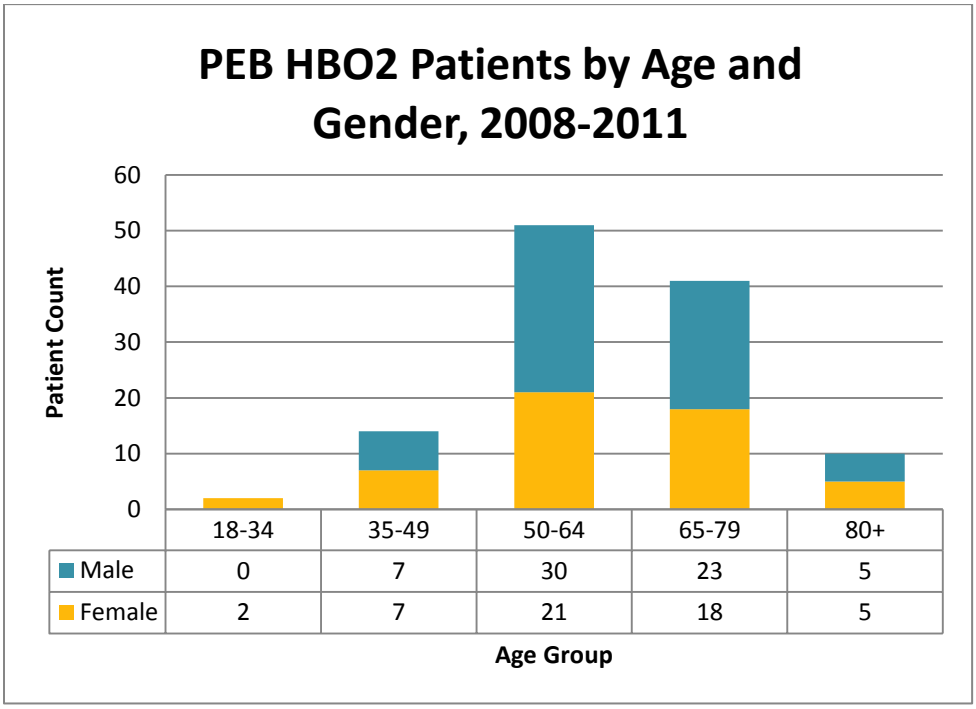


Figure 2b: Medicaid Hyperbaric Oxygen (HBO2) Use by Age and Gender, 2008-2011

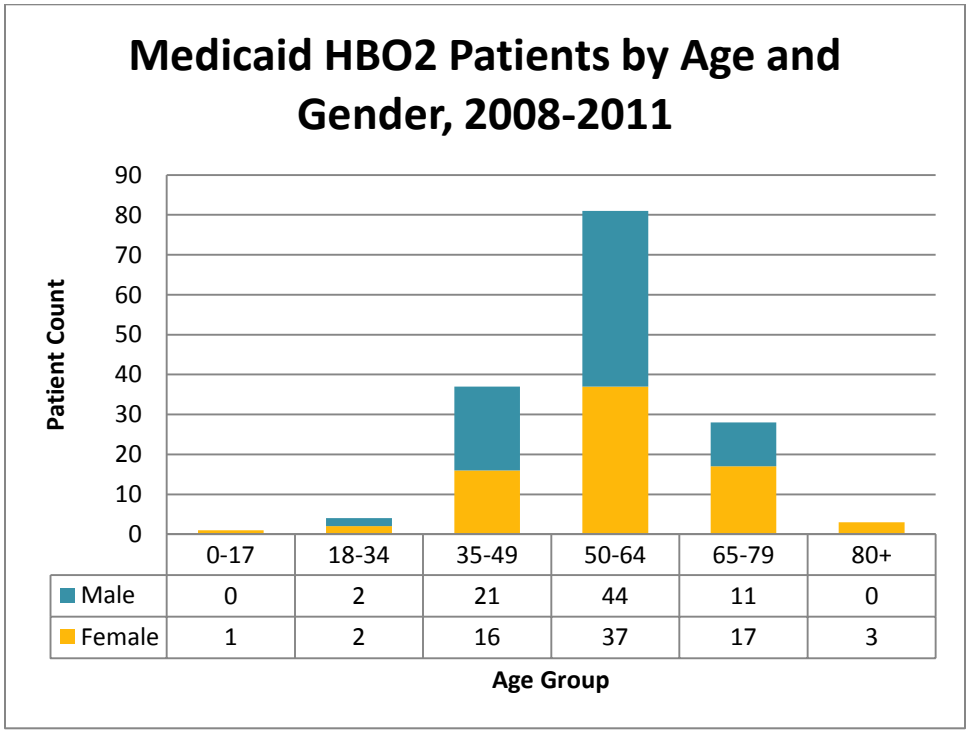
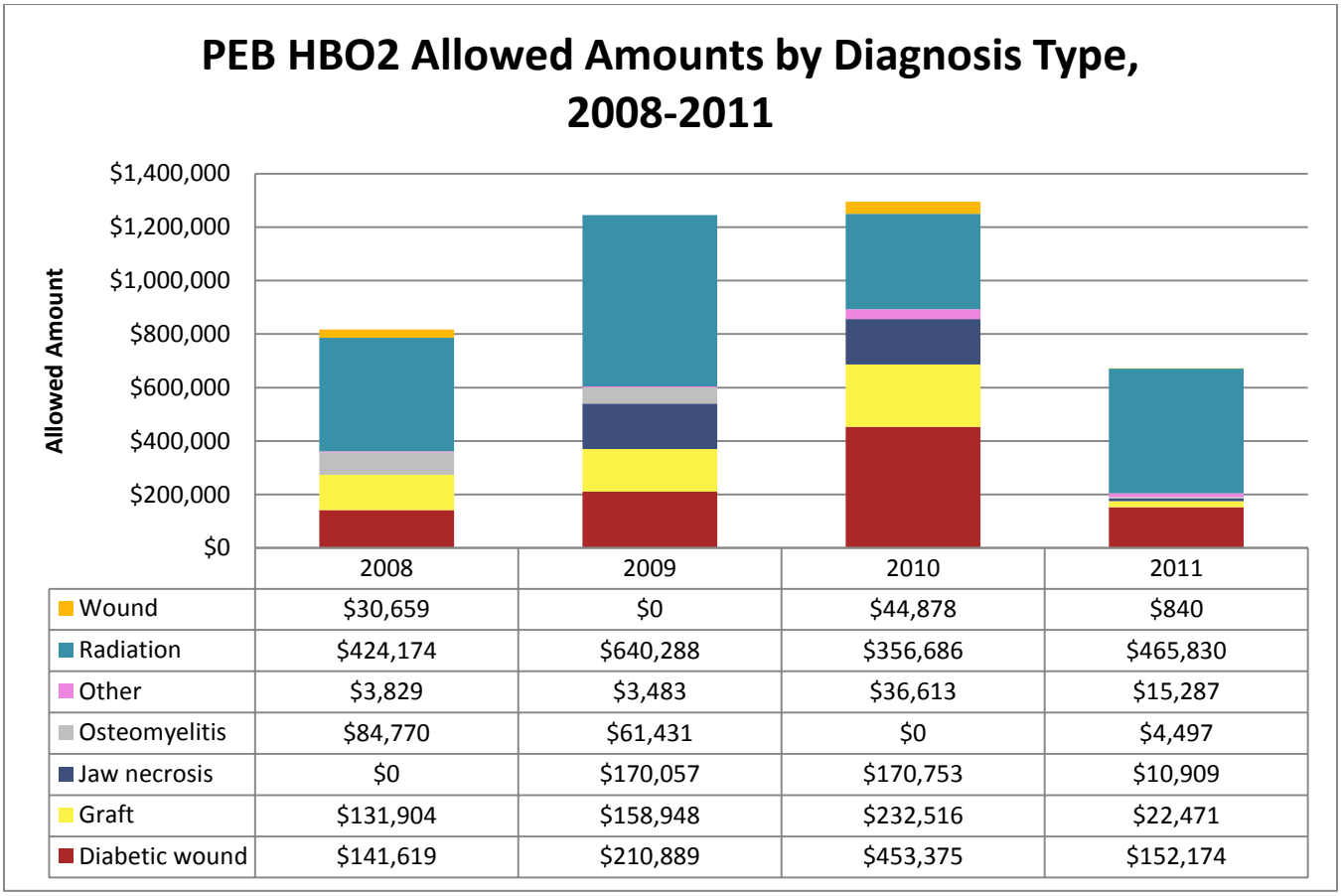


Figure 3: HBO2 Treatment Course Allowed Amounts

Per Patient Average Charges	PEB Primary (No Medicare)	PEB Medicare	Medicaid
Facility vs. Professional charges			
Professional Services	$9,382	$6,649	$1,134
Facility	$18,328	$40,125	$7,156
Average Allowed Amount Per Patient	**$27,710**	**$46,774**	**$8,290**

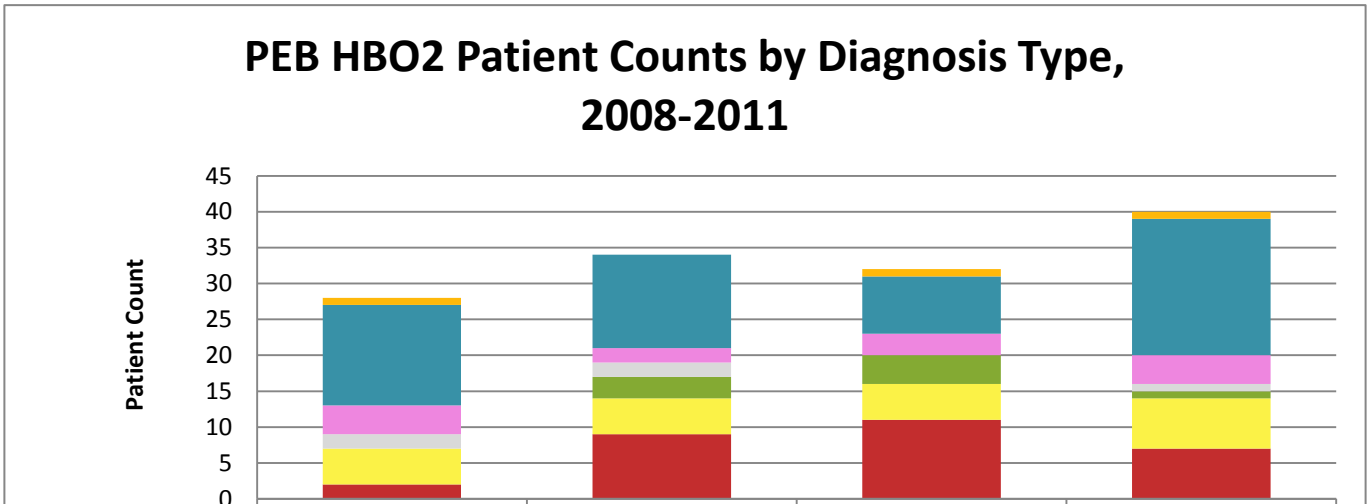
Figure 4a: PEB HBO2 Allowed Amount by Diagnosis Type, 2008-2011



	2008	2009	2010	2011
Wound	$30,659	$0	$44,878	$840
Radiation	$424,174	$640,288	$356,686	$465,830
Other	$3,829	$3,483	$36,613	$15,287
Osteomyelitis	$84,770	$61,431	$0	$4,497
Jaw necrosis	$0	$170,057	$170,753	$10,909
Graft	$131,904	$158,948	$232,516	$22,471
Diabetic wound	$141,619	$210,889	$453,375	$152,174

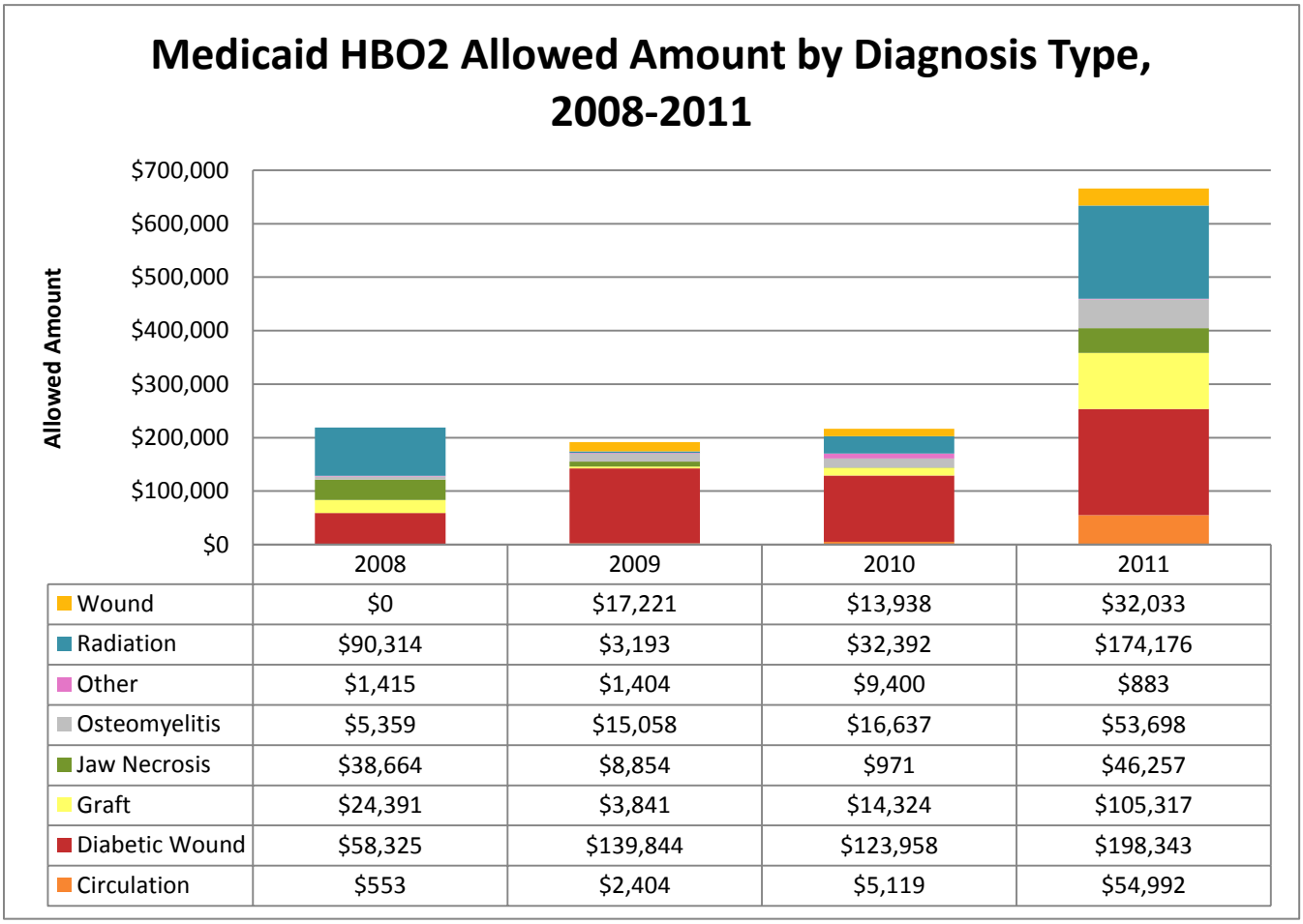
"Other" category includes hearing ($7,500), brain disorders ($6,400), and carbon monoxide/Caisson disease ($4,500).

Figure 4b: PEB Hyperbaric Oxygen Patient Count by Diagnosis Type, 2008-2011



	2008	2009	2010	2011
Wound	1	0	1	1
Radiation	14	13	8	19
Other	4	2	3	4
Osteomyelitis	2	2	0	1
Jaw necrosis	0	3	4	1
Graft	5	5	5	7
Diabetic wound	2	9	11	7

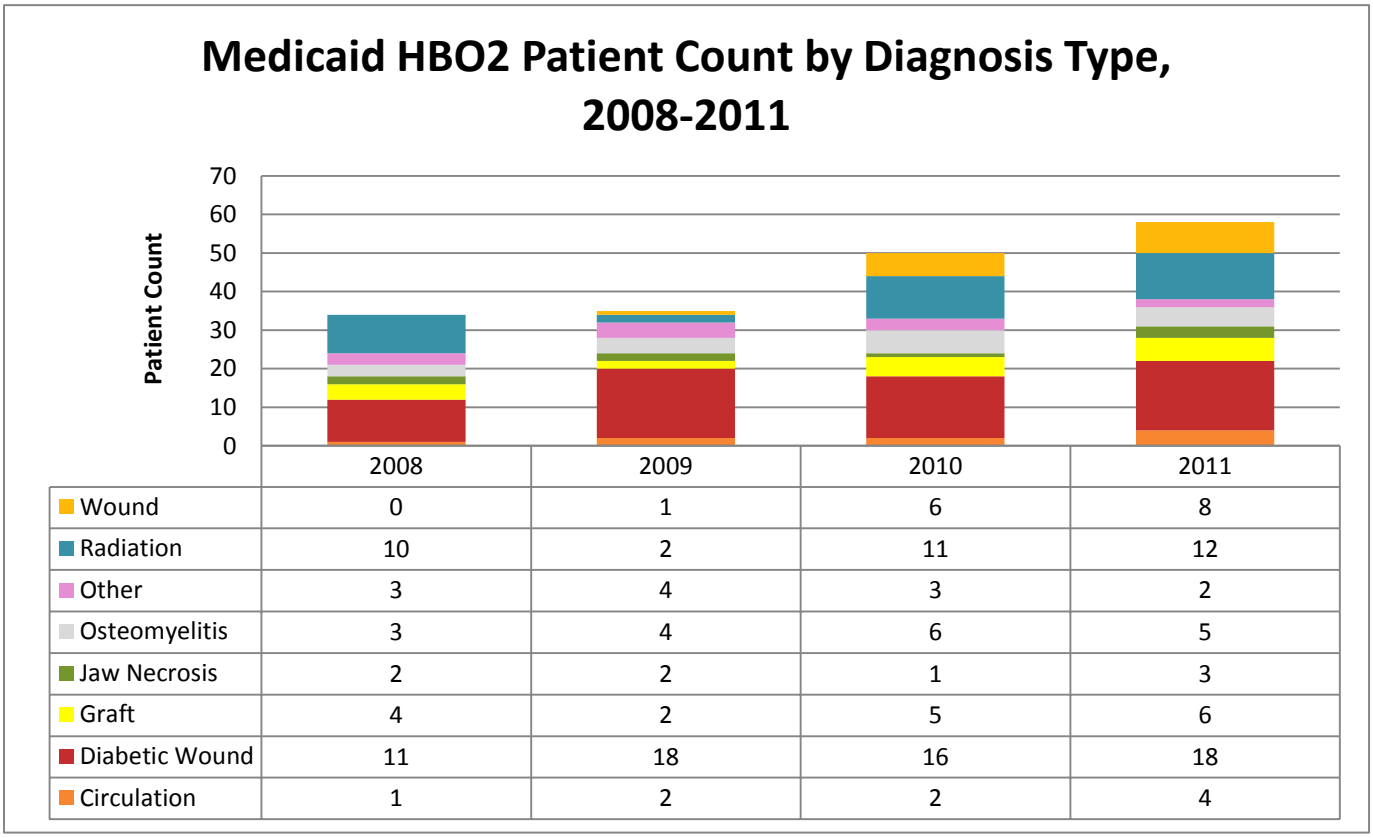
Figure 4c: Medicaid Hyperbaric Oxygen Allowed Amount by Diagnosis Type, 2008-2011



	2008	2009	2010	2011
Wound	$0	$17,221	$13,938	$32,033
Radiation	$90,314	$3,193	$32,392	$174,176
Other	$1,415	$1,404	$9,400	$883
Osteomyelitis	$5,359	$15,058	$16,637	$53,698
Jaw Necrosis	$38,664	$8,854	$971	$46,257
Graft	$24,391	$3,841	$14,324	$105,317
Diabetic Wound	$58,325	$139,844	$123,958	$198,343
Circulation	$553	$2,404	$5,119	$54,992

"Other" category includes neuropathy ($10,000), carbon monoxide/toxic fumes ($1,500), skin disorders ($800) and infection ($700).

Figure 4d: Medicaid Hyperbaric Oxygen Patient Counts by Diagnosis Type, 2008-2011



	2008	2009	2010	2011
Wound	0	1	6	8
Radiation	10	2	11	12
Other	3	4	3	2
Osteomyelitis	3	4	6	5
Jaw Necrosis	2	2	1	3
Graft	4	2	5	6
Diabetic Wound	11	18	16	18
Circulation	1	2	2	4

Figure 5a: PEB HBO2 Treatment Courses by Select Diagnosis Categories

Treatment Category	Patients	Average Treatment Days per Patient	Treatment Days Range	Standard Deviation of Treatment Days	Average Treatment Minutes per Patient	Treatment Minutes Range	Standard Deviation of Treatment Minutes
Radiation	47	**32.7**	3 - 101	20.1	**2,587**	90 – 12,030	2,342
Diabetic Wound	26	**39.6**	3 - 78	18.9	**2,520**	90 – 8,760	2,108
Graft	18	21.3	1 - 61	18.7	1,290	30 – 3,600	1,317
Jaw Necrosis	6	29.2	15 - 53	15.0	**2,770**	450 – 4,620	1,506
Osteomyelitis	4	**37.3**	14 - 62	19.8	2,115	510 – 5,370	2,202
Wound	4	19.3	2 - 40	17.1	2,168	60 – 4,710	2,356
Overall	**118**	**29.4**	**1 - 101**	**20.4**	**2,128**	**30 – 12,030**	**2084**

Figure 5b: Medicaid HBO2 Treatment Courses by Select Diagnosis Categories

Treatment Category	Treatment Courses*	Average Treatment Days per Treatment Course*	Range Treatment Days	Standard Deviation of Treatment Days	Average Treatment Minutes per Treatment Course	Treatment Minutes Range	Standard Deviation of Treatment Minutes
Diabetic Wound	55	**27.9**	1 - 93	22.2	**2,629**	30 – 8,760	2,321
Radiation	38	23.3	1 - 61	17.8	**2,336**	30 – 7,020	2,178
Osteomyelitis	16	22.7	2 - 63	18.1	2,142	60 – 7,380	2,302
Graft	15	19.7	1 - 68	23.5	1,544	30 – 7,500	2,113
Wound	15	12.6	1 - 43	13.8	1,213	30 – 4,830	1,478
Circulation	8	**25.0**	1 - 53	20.6	2,008	30 – 6,000	1,980
Jaw Necrosis	7	**24.3**	1 - 47	17.2	**2,904**	30 – 5,880	2,242
Overall	**173**	**22.8**	**1 - 93**	**20.3**	**2,105***	**30 – 8,760**	**2,196**

***15 Medicaid patients had two or more treatment courses within the four years, some for varying diagnoses. The analysis by treatment course results in a lower overall average treatment days and minutes than shown in Figure 1 (per patient versus per treatment course).

Related Medical Codes

Procedure Code	Description	Type
99183	HYPERBARIC OXYGEN THERAPY	CPT
C1300	HYPERBARIC OXYGEN	HCPCS

Diagnosis Code	Description	Category	Source
250	Diabetes	Diabetic wound	KQ[1]
339	Other headache syndromes	Headache	KQ
340	Multiple sclerosis	Multiple sclerosis	KQ
343	Cerebral palsy	Cerebral palsy	KQ
346	Migraine	Headache	KQ
388	Other disorders of ear, including tinnitis	Hearing	Agency Data
389.16	Sensorineural hearing loss	Hearing	KQ
430 - 432	Intercerebral hemorrhage	Brain	Agency Data
526.89	Jaw disease	Jaw necrosis	Agency Data
558.1	Radiation enterocolitis	Radiation	KQ
707 - 707.9	Ulcers, chronic ulcers (except varicose)	Wound	KQ
730-730.2	Osteomyelitis, acute, chronic & unspecified	Osteomyelitis	KQ
784	Headache	Headache	KQ
890 - 894	Open wounds	Wound	KQ
909.2	Late effects of radiation	Radiation	KQ
940 - 949.5	Burns	Wound	KQ
986	Toxic effects of carbon monoxide	Toxic fumes	Agency Data
990	Effects of radiation	Radiation	KQ
993	Effects of air pressure (bends, etc)	Caisson's disease	Agency Data
996	Complications of graft or prosthetic (implanted)	Graft	KQ
997.6	Amputation stump complication	Wound	Agency Data
998.3	Disruption of surgical wound	Wound	KQ

1 KQ = Key Questions

TECHNOLOGY DESCRIPTION

Hyperbaric oxygen therapy (HBOT) involves the therapeutic administration of 100% oxygen at environmental pressures greater than 1 atmosphere absolute (ATA), the atmospheric pressure at sea level. Administering oxygen at pressures greater than 1 ATA requires compression. This is achieved by placing the patient in an airtight chamber, increasing pressure inside the chamber, and administering 100% oxygen for respiration, which delivers a greatly increased pressure of oxygen to the lungs, blood, and tissues. Often, these treatments involve pressurization from 2.0 to 2.5 ATA for periods of 60 to 120 minutes once or twice daily for a total of 30 to 60 treatment sessions. There are 2 types of chambers used for administering HBOT: a monoplace chamber for a single patient; or a multiplace chamber used for multiple patients and medical personnel. In a multiplace hyperbaric oxygen (HBO) chamber, patients inhale the pressurized oxygen through a hood or mask, as opposed to inhaling it directly, as is the case in an oxygen-filled monoplace chamber.

No standard protocol has been identified for HBOT sessions. Regardless of the type of chamber used, the interval between sessions and the total number of treatments varies according to the severity of the condition and physician preference. Treatment may begin with 1 to 3 treatments per day for up to 1 week and may continue daily for several days to several months. For each treatment, the pressure in the chamber is increased slowly and then held constant for 30 minutes to several hours. An air break is given during treatment sessions, during which the patient breathes atmospheric air at the elevated chamber pressure to decrease the risk of an oxygen toxicity seizure or other side effects. At the end of the treatment session, the chamber pressure is decreased gradually to ambient atmospheric pressure since a rapid decrease could cause decompression sickness and severe inner ear damage (Schaefer, 1992; Tomaszewski and Thom, 1994; Whelan and Kindwall, 1998; Vahidova et al., 2006).

REVIEW OBJECTIVES

The scope of this report is defined by the following **PICO statement**:

Populations: Adults and children with the following indications for HBOT:

- Diabetic nonhealing wounds, including foot ulcers.
- Other nonhealing wounds, including skin and tissue grafts, thermal burns, and surgical wounds.
- Refractory osteomyelitis.
- Late radiation tissue injury (LRTI).
- Brain injury.
- Cerebral palsy.
- Headache/migraine.
- Multiple sclerosis (MS).
- Sensorineural hearing loss.

Intervention: Hyperbaric oxygen therapy delivered via a hyperbaric oxygen chamber

Comparators: Standard treatment alone, a competing alternative, or sham treatments

Outcomes: Patient-centered outcomes, including:

- Incidence of healing
- Time to healing
- Secondary wound closure
- Infection rates
- Wound recurrence
- Pain
- Disease-specific patient-centered health outcomes
- Mortality
- Depression

The following key questions will be addressed:

1. Is HBOT effective in improving patient-centered outcomes for individuals with the following conditions:
   - Diabetic nonhealing wounds, including foot ulcers.
   - Other nonhealing wounds, including skin and tissue grafts, thermal burns and surgical wounds.
   - Refractory osteomyelitis.
   - Late radiation tissue injury (LRTI).
   - Brain injury.
   - Cerebral palsy.
   - Headache/migraine.
   - Multiple sclerosis (MS).
   - Sensorineural hearing loss.

1a. What is the optimal frequency, dose, and duration of HBOT treatment?

2. What harms are associated with HBOT?
3. What is the differential effectiveness and safety of HBOT according to factors such as age, sex, race or ethnicity, disability, comorbidities, wound or injury duration and severity, and treatment setting?
4. What are the cost implications of HBOT, including the cost-effectiveness compared with alternative treatments?

METHODS

Search Strategy for Systematic Reviews and Health Technology Assessments

During a period of topic scoping and key question refinement, we determined that the volume of available literature on hyperbaric oxygen therapy (HBOT) was too great for a detailed analysis of all relevant primary data for each indication under investigation. Consequently, we conducted a systematic search for systematic reviews and health technology assessments (HTAs) to answer each key question and manually searched each included review for additional relevant studies. Appendix I outlines the search strings employed. In addition, we systematically searched for primary data published subsequent to the selected systematic reviews for each indication and searched for all harms studies published over the last 10 years. We began with a search of the MEDLINE, Cochrane, York University Center for Reviews and Dissemination (CRD), and Embase databases on June 20, 2012. We used the MeSH term for hyperbaric oxygen in PubMed, and "hyperbaric oxygen" as a text word in the Cochrane, CRD, and Embase databases. PubMed and Embase results were filtered using the systematic reviews, meta-analyses, reviews, and practice guidelines filter in PubMed and the "best balance between sensitivity and specificity reviews" filter in Embase. The results were also limited to human studies in the English language published from 2002 to June 2012. Despite these filters, the Embase search yielded more than 1300 reviews. Upon scanning a random selection of the Embase results, it became obvious that the yield of additional relevant systematic reviews would be very small and that all relevant systematic reviews could be obtained through a combination of PubMed, Cochrane, CRD, and by manually searching relevant articles. The Embase results were therefore restricted by searching the results using a selection of key terms for each indication under investigation.

An update search was conducted on November 8, 2012. The MEDLINE and Embase databases were searched for RCTs and meta-analyses published since June 2012.

Selection of Systematic Reviews and HTAs

Title and abstracts from the combined searches were reviewed for relevance according to the predefined inclusion and exclusion criteria outlined below. Subsequently, the full texts of each included study were retrieved and reviewed using the same inclusion and exclusion criteria. Relevant data from the selected systematic reviews and HTAs were abstracted into evidence tables for inclusion in the report (Appendixes III and V). The excluded studies are listed in Appendix VI, and a summary of exclusion reasons is provided in Figure 1 in the findings section.

Inclusion criteria: These include English-language systematic reviews or HTAs published between 2002 and 2012, investigating the effectiveness, safety, cost, or guidelines associated with HBOT for the indications under investigation.

Exclusion criteria: The following criteria were used to exclude studies not relevant to the report:

1. Study not a systematic review or HTA:
2. Wrong population
3. Wrong intervention
4. Wrong outcome
5. Later systematic review exists from the same author or group

6. Represents a paper publication from an already included systematic review
7. Systematic review covered more adequately by another review
8. A guideline not of interest to the report
9. Wrong study design from the supplemental primary data search

Search Strategy and Selection of Primary Data and Harms Studies

Following identification and selection of systematic reviews and HTAs, we undertook a targeted search of MEDLINE for relevant primary data studies published subsequent to the review(s) selected for each indication. We limited the search to human clinical trials published in the English language. At the same time, we conducted a search of MEDLINE for harms-specific HBOT studies published in the last 10 years. We did not limit the harms data search by study design. As before, title, abstracts, and full texts were reviewed using the relevant inclusion and exclusion criteria described above and data were abstracted into evidence tables for inclusion in the report.

Search Strategy and Selection of Guidelines/HBOT Coverage Policies

In addition to guidelines found through the database and manual searches outlined above, we also searched the National Guidelines Clearinghouse. Guidelines were not abstracted into evidence tables but rather summarized descriptively in the report. At the direction of Washington State HCA, we searched the CMS, Aetna, Regence BCBS, and Group Health websites for coverage policies relevant to this report. Relevant coverage policies were summarized in the report.

Other Searches

The Hayes Knowledge Center was searched for reports on HBOT. Relevant reports were used as background, for identifying relevant primary data studies not included in the selected published systematic reviews and as a source of harms data. The Hayes reports were not abstracted into evidence tables; pertinent data were included under the relevant sections of the report.

Quality Assessment

We conducted quality assessments throughout the process. We rated the quality of each systematic review using the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Shea et al., 2007). This quality assessment for systematic reviews was particularly important for those reviews that carried out pooled data analysis. However, we also found value in quality rating the systematic reviews that did not conduct meta-analyses because the quality rating provided guidance on how confident we could be of the quality assessment for individual studies conducted by the review authors. Poor-quality systematic reviews were included because, although the methodological rigor of the systematic review was poor, many reviews included fair and good-quality individual studies useful to the report. We rated the quality of individual studies using Hayes criteria (see Appendix II). We did not rate the full-text versions of each primary data study, rather, we judged the effectiveness of the quality assessment tool employed in each systematic review and applied the Hayes checklist for quality to confirm the quality rating provided by the author. In cases where we deemed it necessary to change a quality rating, we retrieved the full-text version to confirm our decision. We then graded the overall quality of the evidence by indication according to risk of bias (individual study quality); consistency of results across studies; precision (the

degree of certainty around the effect estimate)and applicabaility[1] of the evidence to the populations, interventions, comparators, health outcomes, and, if specified, settings of interest; and quantity of data (number of studies and sample sizes). In addition, we rated the quality of the clinical guidelines using the Appraisal of Guidelines Research and Evaluation (AGREE) tool (AGREE Enterprise, 2009).

Appendix II describes the steps involved in the quality assessment process. Hayes uses internally developed Quality Checklists for individual studies, which address study design, integrity of execution, completeness of reporting, and the appropriateness of the data analysis approach. Individual studies were rated as *good*, *fair*, *poor*, or *very poor*. The quality of a body of evidence for a particular outcome or indication was graded as *high*, *moderate*, *low*, or *very low*, which can be defined as follows:

> **High:** Suggests that we can have high confidence that the evidence found is reliable, reflecting the true effect, and is very unlikely to change with the publication of future studies
>
> **Moderate:** Suggests that we can have reasonable confidence that the results represent the true direction of effect but that the effect estimate might well change with the publication of new studies
>
> **Low:** We have very little confidence in the results obtained, which often occurs when the quality of the studies is poor, the results are mixed, and/or there are few available studies. Future studies are likely to change the estimates and possibly the direction of the results.
>
> **Very low***:* Suggests no confidence in any result found, which often occurs when there is a paucity of data or the data is such that we cannot make a statement on the findings.

[1] Two terms related to applicability are *directness* and *generalizability.* Directness refers to how applicable the evidence is to the outcomes of interest (i.e., surrogate or intermediate outcomes versus health outcomes) or to the comparator of interest (indirect comparison of two treatments versus head-to-head trials). Generalizability usually refers to whether study results are applicable to the populations or settings of interest.

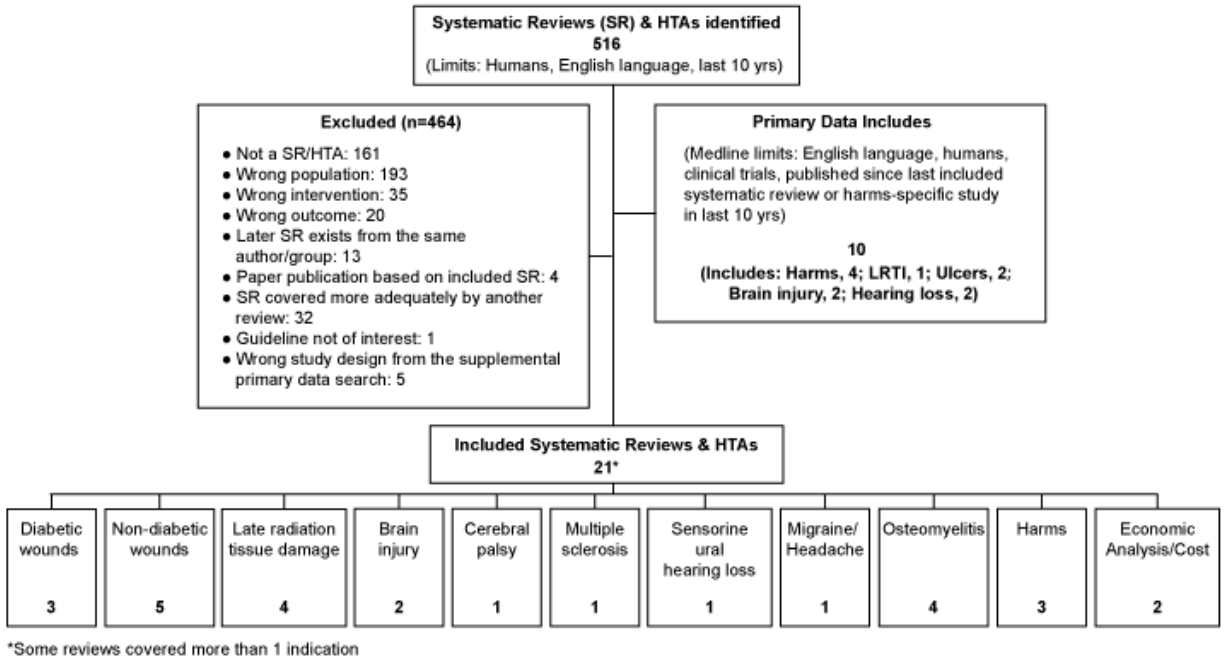
LITERATURE REVIEW

Search Results

Figure 1 details the systematic identification and selection of materials included in this report. We found 21 systematic reviews meeting predefined inclusion criteria. Also included are 4 harms-specific primary data studies and 5 primary data studies covering a range of indications of interest and identified through a search for studies published subsequent to the included systematic reviews. The 31 total included studies cover 156 primary data studies. Several reviews were cross-cutting in nature, covering more than one indication or key question (KQ). Figure 1 also provides details of studies and reviews that were excluded from the report.

Additional search result details are presented in the discussion of findings for each key question. In addition, Appendixes III to V present detailed tables of study characteristics and results.

Figure 1. Systematic Identification and Selection of Evidence



*Some reviews covered more than 1 indication

An update search was conducted on November 8, 2012. The MEDLINE and Embase databases were searched for randomized controlled trials (RCTs) and meta-analyses published subsequent to the original search. The update search uncovered one new RCT on the efficacy of hyperbaric oxygen therapy (HBOT) in the management of chronic nonhealing ulcers (Kaur et al., 2012). The results of the study did not change the overall findings of the report and the study was not abstracted into the evidence tables. The results of the study are included in KQ1 and the study is included in the overall count of selected evidence (see Figure 1).

Key Questions and Findings

Key Question #1: Is HBOT effective in improving patient-centered outcomes for individuals with the following conditions?

Table 1 summarizes search results for the studies selected to answer KQ1. Sixteen selected systematic reviews included 133 primary data studies. A further 5 primary data studies were found through a search of the literature published subsequent to the chosen systematic reviews (including 1 RCT found during the update search), bringing the total number of included primary data studies to 138 (7225 participants). Of the included studies, 61 were RCTs, 4 were nonrandomized controlled trials, 8 were pre-post studies (7 uncontrolled, 1 with historical controls), and 64 were other observational studies, including prospective and retrospective cohorts as well as case series.

Table 1. Search Results for KQ1

Indication	# Included Systematic Reviews	# Primary Studies*	Study Design	Total Sample Size
Diabetic nonhealing wounds	3	16	RCTs: 8 Nonrandomized controlled trials: 2 Observational studies†: 6	1437
Other nonhealing wounds	5	17	RCTs: 8 Observational studies†: 9	806
Late radiation tissue injury	4	35	RCTs: 13 Observational studies†: 22	1664
Refractory osteomyelitis	4	23	RCTs: 0 Nonrandomized controlled trials: 2 Observational studies†: 21	510
Brain injury	2	16	RCTs: 6 Pre-post studies: 4 Other observational designs: 6	1283
Cerebral palsy	1	6	RCTs: 2 Pre-post studies: 4	449
Headache/migraine	1	7	RCTs: 7	119
Multiple sclerosis	1	9	RCTs: 9	504
Sensorineural hearing loss	1	8	RCTs: 8	453
Total	**16 systematic reviews(some cover multiple indications)**	**138**	**RCTs: 61** **Nonrandomized controlled trials: 4** **Uncontrolled pre-post studies: 8** **Observational studies†: 64**	**7195**

*Including primary data studies in each systematic review and additional peer-reviewed studies published subsequent to the systematic reviews and meeting inclusion criteria.
†Includes uncontrolled prospective and retrospective cohort studies and case series.

HBOT for Diabetic Nonhealing Wounds, Including Foot Ulcers

Three systematic reviews (1437 participants), including 16 peer-reviewed studies (8 RCTs, 2 nonrandomized controlled trials, and 6 observational studies), reported on the effectiveness of HBOT for the treatment of diabetic nonhealing wounds (Wang et al., 2003; Goldman, 2009; Kranke et al., 2012).

All of the studies involved diabetic foot ulcer patients and the outcomes evaluated included incidence of healing, wound size reduction, amputation rates, and quality of life.

Findings by Outcome

Incidence of Healing: A good-quality 2012 Cochrane Review by Kranke and colleagues identified 8 RCTs (Doctor et al., 1992; Faglia et al., 1996; Lin et al., 2001; Abidia et al., 2003; Kessler et al., 2003; Duzgun et al., 2008; Löndahl et al., 2010; Wang et al., 2011) evaluating the effectiveness of HBOT for the treatment of diabetic foot ulcers (Kranke et al., 2012). Pooled analysis of data from 3 trials (Abidia et al., 2003; Kessler et al., 2003; Löndahl et al., 2010) (140 participants) found that the addition of HBOT to standard wound treatment results in a significant improvement in healing at 6 weeks follow-up (RR, 5.2; 95% CI, 1.25-21.66; absolute risk difference, 12.2%; NNT, 8) and although this benefit was not significant at 12 months (RR, 9.53; 95% CI, 0.44-207.76), the authors caution that the 12-month pooled estimate may not be accurate because of heterogeneity among studies. A poor-quality systematic review by Goldman (2009), also evaluated the benefit of HBOT for wound healing and limb salvage among patients with diabetic foot ulcers but did not restrict study design to RCTs (Goldman, 2009). Among 10 included studies (1055 participants), 4 were RCTs (all of which appeared in the later Cochrane Review), 3 were prospective cohort studies, 2 were retrospective cohort studies, and 1 was a case series. Pooled analysis of 6 studies (138 participants) reported an odds ratio (OR) of 9.992 (95% CI, 3.972-25.132) in favor of HBOT for improved healing. However, this result must be interpreted with great caution because we believe the pooling of the studies in question was inappropriate due to significant heterogeneity between the studies and poor internal validity of at least one included study. We chose to include the Goldman review in our analysis because despite our reservations regarding the appropriateness of the meta-analysis conducted by the author, we see value in including the individual study results based on the assumption that observational data may be more generalizable to the population of patients with nonhealing diabetic wounds and, therefore, provide value in terms of applicability. Among 2 fair-quality prospective cohort studies included by Goldman and colleagues, one found HBOT to be more effective than no HBOT for the healing of diabetic foot ulcers and one reported no significant difference in receiving or not receiving HBOT (Goldman, 2009). Specifically, Zamboni et al. (1997) reported significant healing at the end of a 7-week treatment period among patients receiving HBOT compared with non-HBOT receiving patients (P<0.05); and Kalani et al. (2002) found no difference between those receiving or not receiving HBOT (Goldman, 2009). An earlier fair-quality HTA by Wang and colleagues included 6 of the studies already discussed (and published at that time) as well as an additional 2 very-poor-quality case series with both observing high complete healing rates among patients receiving HBOT as an adjunct to standard wound treatment (75% and 88% complete healing, respectively) (Wang et al., 2003). The report concluded that HBOT aids in wound healing for nonhealing diabetic wounds.

Amputation Rates: The 2012 Cochrane Review pooled data from 5 trials (Doctor et al., 1992; Faglia et al., 1996; Abidia et al., 2003; Duzgun et al., 2008; Löndahl et al., 2010) (309 participants) and showed a trend toward a benefit from HBOT in the rate of major amputations but no statistically significant difference between the groups (RR, 0.36; 95% CI, 0.11-1.18) (Kranke et al., 2012). It should, however, be noted that 1 of the 5 included studies excluded participants at high risk for major amputations (Löndahl et al., 2010). When this study was excluded from the analysis, the benefit of HBOT became significant (P=0.009). HBOT provided no additional benefit in the rate of minor amputations (RR, 0.76; 95% CI, 0.19-3.10) (Kranke et al., 2012). In a meta-analysis of 7 studies, including 3 RCTs (Doctor et al., 1992; Faglia et al., 1996; Abidia et al., 2003), 2 prospective cohorts (Baroni et al., 1987; Kalani et al., 2002), and 2 retrospective cohorts (Oriani et al., 1990a; Faglia et al., 1998), Goldman (2009) reported reduced odds of

amputation among patients receiving HBOT compared with those not receiving HBOT (OR, 0.242; 95% CI, 0.137-0.428). However, for the reasons described above, we have very low confidence in the validity of this odds ratio but included the review for the value provided by the individual study results. Among 2 fair-quality studies included by Goldman and colleagues and not included in the later Cochrane Review, one reported significantly fewer amputations among patients receiving HBOT (14% versus 31%; *P*=0.012) (Faglia et al., 1998), and one found no statistically significant reduction in amputation rates (12% among HBOT group versus 33%; *P*=NS) (Kalani et al., 2002).

Wound Size Reduction: The 2012 Cochrane Review found 1 fair-quality RCT (Kessler et al., 2003), which reported a 41.8% reduction in wound size at 2 weeks posttreatment among the HBOT group compared with 21.7% in the control group (*P*=0.04). However, the mean difference (MD) between groups became nonsignificant at 4 weeks (MD, 6.4%; 95% CI, –15.3 to 28.1) (Kranke et al., 2012).

QOL: Kranke et al. (2012) reported on QOL as an outcome of interest in the 2012 Cochrane Review. They reported that in 1 good-quality RCT (n=94) (Löndahl et al., 2010), no significant difference was found in overall physical summary scores between the HBOT and control groups at 1-year follow-up (MD, –0.2; 95% CI, –8.58 to 8.18). Similarly, no significant difference was found in overall mental health summary scores (MD, 6.60; 95% CI, –3.93 to 17.13) (Kranke et al., 2012).

Quality Assessment

Systematic Reviews: Applying AMSTAR criteria for rating the quality of systematic reviews, 1 of 3 selected systematic reviews was considered of good quality (Kranke et al., 2012), 1 fair quality (Wang et al., 2003) and 1 was considered poor quality (Goldman, 2009).

Individual Studies: Each review differed significantly in the approach to rating the quality of individual studies. The review by Kranke et al. (2012) employed the Cochrane Collaborations well-recognized risk of bias assessment criteria for RCTs, and by our assessment made effective use of the tool. Goldman (2009) included nonrandomized controlled trials, cohort studies, and case series in his review and employed the equally well-recognized GRADE (Grades of Recommendation, Assessment, Development and Evaluation) criteria as the quality assessment tool. It is our opinion however, that Goldman did not apply the GRADE tool effectively, inappropriately rating case series and sometimes retrospective cohort studies as moderate quality when it is our belief that the appropriate rating should have been poor for the studies in question. Wang et al. (2003) made no attempt to rate the quality of individual studies in their HTA report; however, all but 2 of the studies included by Wang and of interest to this report had been quality rated by the other authors. Applying the Hayes quality checklist system for rating the quality of individual studies, Table 2 provides the results of our quality assessment. We rated the quality of individual studies as fair overall. The most common reasons for assigning a poor-quality rating was high attrition, poor blinding in RCTs, and the risk of selection bias in observational studies.

Body of Evidence: Table 2 presents the results for the overall quality of evidence. We graded the overall body of evidence for the effectiveness of HBOT for the treatment of diabetic wounds as moderate. Incidence of healing, and amputation rates were considered the major clinical outcomes and therefore carried more weight in the overall quality assessment decision. Individual study quality, consistency, and directness of results account for the overall moderate-quality grade assigned. Wound size reduction and QOL received very low and low grades, respectively, reflecting the paucity of good-quality studies investigating these outcomes.

Summary: Effectiveness of HBOT for diabetic nonhealing wounds, including foot ulcers

Moderate-quality evidence from 3 systematic reviews (1437 participants), including 16 peer-reviewed studies reporting on the effectiveness of HBOT for the treatment of diabetic foot ulcers, suggests that the addition of HBOT to standard wound care promotes wound healing and limb salvage in the short term, with no improvement evident beyond 1 year. The results are clinically meaningful, with pooled data from 3 studies suggesting that 8 patients would need to be treated with HBOT as an adjunct to standard wound care for an additional 1 person to have complete wound healing. There is low-quality evidence suggesting no benefit from HBOT for QOL and insufficient evidence to determine the effectiveness of HBOT for wound size reduction.

Table 2. Summary of Evidence by Outcome for HBOT as a Treatment for Diabetic Nonhealing Wounds, Including Diabetic Foot Ulcers

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Incidence of healing	Benefit at 6 weeks, not significant at 1 year	1 good, 4 fair, 5 poor, 2 very poor	Moderate
Amputation rates	Benefit	1 good, 3 fair, 3 poor	Moderate
Wound size reduction	Benefit at 2 weeks, not significant at 4 weeks	1 fair	Very low
Quality of life	No benefit	1 good	Low

HBOT for Other Nonhealing Wounds, Including Skin and Tissue Grafts, Thermal Burns, and Surgical Wounds

Five systematic reviews (776 participants), including 16 peer-reviewed studies (7 RCTs, and 9 observational studies), reported on the effectiveness of HBOT for the treatment of nondiabetic nonhealing wounds (Wang et al., 2003; Villanueva et al., 2004; Goldman, 2009; Eskes et al., 2010; Kranke et al., 2012). The wounds included arterial, pressure, and venous ulcers; flaps and grafts; crush injuries; surgical reconstruction (without grafts or flaps); and thermal burns. The outcomes evaluated included incidence of healing, time to healing, reduction in wound size, amputation rates, survival of flap or graft, length of hospital stay, mortality, and number of surgeries. Two studies provided detail specific to KQ3 (Mathieu et al., 1990; Grolman et al., 2001) and are discussed in detail in that section but are quality rated here. Meta-analysis was inappropriate due to significant heterogeneity between the studies, so most reviews provided a descriptive analysis of individual study results.

Findings by Type of Wound

Incidence of healing or reduction in wound size among patients with venous, arterial or pressure ulcers: Two of the 5 included systematic reviews reported on the incidence of healing among patients with venous, arterial, or pressure ulcers (Goldman, 2009; Kranke et al., 2012) (51 patients). Kranke and colleagues, in their 2012 Cochrane Review, found no data on arterial or pressure wounds and reported on just 1 small, fair-quality RCT (n=16) that examined the effect of HBOT on the treatment of venous wounds (Kranke et al., 2012). The trial found a significant reduction in venous wound area among patients receiving HBOT versus controls at 6 weeks follow-up (MD, 33%; 95% CI, 18.97-47.03) but no difference at 18 weeks (MD, 29.6%; 95% CI, –23 to 82.2). They found no significant difference between groups in the proportion of ulcers completely healed at any time (Hammarlund and Sundberg, 1994). Goldman (2009) expanded his systematic review to include study designs other than RCTs, and in

addition to the trial by Hammarlund and Sundberg, described above, reported a small poor-quality case series of 35 patients with leg ulcers, 80% of whom showed compete wound healing following HBOT (Efrati et al., 2007). The update search uncovered one additional RCT that investigated the efficacy of HBOT in the management of chronic nonhealing ulcers (Kaur et al., 2012). This was a small trial, of fair quality, including 30 patients with a variety of ulcer types randomized to HBOT plus conventional treatment or conventional treatment alone. Following 30 days of treatment, there was a 59% reduction in wound area in the HBOT group compared with a 26% increase in wound area in the control group (*P*=0.001).

Incidence of healing, time to healing, and amputation rates among patients with crush injuries: Two of the 5 included systematic reviews reported on these outcomes among patients with crush injuries (Wang et al., 2003; Eskes et al., 2010). Both reviews reported the same fair-quality RCT of 36 patients, which found significantly more complete healing among the HBOT group (94% complete healing) compared with controls (56% complete healing) (RR, 1.7; 95% CI, 1.11-2.61; NNT, 3), no significant difference with regard to mean time to healing among the HBOT group (50.2 days) versus controls (55.8 days) (MD, 5.6 days; 95% CI, –19 to 7.8), no significant difference with regard to the number of amputations among the HBOT group (0) versus controls (2) (RR, 0.2; 95% CI, 0.01-3.89), and no significant difference in mean length of hospital stay among the HBOT group (22.4 days) versus controls (22.9 days) (MD, –5.0; 95% CI, –9.96 to 8.96) (Bouachour et al., 1996).

Incidence of healing among patients having undergone surgical reconstruction (without grafts or flaps): Goldman (2009) included 2 fair-quality prospective cohort studies (84 patients) evaluating the effectiveness of HBOT on healing among patients having undergone surgical reconstruction (without grafts or flaps) (Zhao et al., 1991; Reedy et al., 1994). One study reported 89% improved healing in the HBOT group versus 73% among controls (*P*<0.05) (Zhao et al., 1991); the other reported breakdown and infection in 1 patient receiving HBOT (17%) versus 7 patients (78%) not receiving HBOT (*P*<0.01) (Reedy et al., 1994).

Incidence of wound recovery and healing among patients with acute traumatic peripheral ischemia: One systematic review (Wang et al., 2003) reported one case series, which reported improved wound recovery and complete healing among a series of 23 patients who received HBOT as an adjunct therapy (Mathieu e al., 1990). The study did not provide detailed data.

Graft and flap survival/take and healing: Three of the 5 included reviews reported on these outcomes among 425 patients with compromised skin grafts or flaps. (Wang et al., 2003; Goldman, 2009; Eskes et al., 2010) The 2010 Cochrane Review by Eskes and colleagues included 2 poor-quality RCTs, which examined the effectiveness of HBOT for improving graft or flap survival among patients with acute surgical and traumatic wounds (Perrins, 1967; Xie and Li, 2007). Perrins (1967) looked at HBOT versus usual care for split skin grafts (n=48) and found significantly better graft survival among the HBOT group (64%) compared with the usual care group (17%) (RR, 3.5; 95% CI, 1.35-9.11; NNT, 2) (Perrins, 1967). Xie and Li (2007) compared HBOT with dexamethasone and heparin among 155 patients with skin defects in the limbs who underwent flap grafting. They found that HBOT was no better than dexamethasone for complete flap survival (89% versus 78%, respectively) (RR, 1.14; 95% CI, 0.95-1.38). Similarly, HBOT was not significantly better than local heparin for complete flap survival (89% versus 73%, respectively) (RR, 1.21; 95% CI, 0.99-1.49) (Xie and Li, 2007). Goldman (2009) included 3 poor-quality case series (47 patients) in his review, evaluating graft take among patients having undergone HBOT before and /or after skin grafting (Gonnering et al., 1986; Saber et al., 2005; Friedman et al., 2006) and 1 poor-quality

case series of 15 patients having received HBOT as an adjunct treatment for compromised flaps (Mathieu et al., 1993). One reported 50% complete graft take at 18-month follow-up (Saber et al., 2005); 2 reported 100% graft take (Gonnering et al., 1986; Friedman et al., 2006) and 1 reported complete flap healing (Mathieu et al., 1993). The Wang et al. (2003) review reported one other (unpublished) unknown-quality RCT providing evidence of HBOT effectiveness for the healing of compromised skin grafts. Marx (1994) (160 patients) reported delayed wound healing among the HBOT group of 11% versus 55% in the control group (RR, 0.2; *P*=0.001).

Mortality, mean time to healing, graft take, number of required surgeries, and length of hospital stay among patients with thermal burns: One Cochrane Systematic Review, including 2 fair-quality RCTs, reported on the effectiveness of HBOT among 141 patients with thermal burns (Villanueva et al., 2004). After adjusting for the patient's condition, one trial found no significant differences in length of hospital stay, mortality (11% in each group), or number of surgeries between the HBOT and control groups (Brannen et al., 1997). The other trial reported significantly better time to healing among the HBOT group (19.7 days) compared with the control group (43.8 days) (*P*<0.001) (Hart et al., 1974).

Quality Assessment

Systematic Reviews: Applying AMSTAR criteria for rating the quality of systematic reviews, 3 of 5 selected systematic reviews were considered good-quality reviews (Villanueva et al., 2004; Eskes et al., 2010; Kranke et al., 2012), one was considered fair quality (Wang et al., 2003), and one was considered poor quality (Goldman, 2009).

Individual Studies: The 3 Cochrane Systematic Reviews (Villanueva et al., 2004; Eskes et al., 2010; Kranke et al., 2012) employed the Cochrane Collaboration risk of bias assessment criteria for RCTs, and by our assessment, made effective use of the tool. Goldman (2009) included nonrandomized controlled trials, cohort studies, and case series in his review and employed GRADE criteria as the quality assessment tool. It is our opinion, however, that Goldman did not apply the tool effectively, inappropriately rating case series and sometimes retrospective cohort studies as moderate quality when it is our belief that the appropriate rating should have been poor for the studies in question. Wang et al. (2003) made no attempt to rate the quality of individual studies in their HTA report; however, all but 2 of the studies included by Wang and of interest to this report had been quality rated by the other authors.

Applying the Hayes quality checklist system for rating the quality of individual studies, Table 3 provides the results of our quality assessment. We rated the overall quality of individual studies as fair. The most common reasons for assigning a poor-quality rating was high attrition, poor blinding in RCTs, and the risk of selection bias in observational studies.

Body of Evidence: Table 3 presents the results for the overall quality of evidence examining the effectiveness of HBOT for the treatment of nonhealing wounds other than diabetic wounds. We graded the overall body of evidence as low quality. Insufficient data, poor consistency in the estimate of effects between outcomes, as well as a high risk of bias in some key studies are the main reasons for the low quality of evidence grade.

Summary: Effectiveness of HBOT for other nonhealing wounds, including skin and tissue grafts, thermal burns, and surgical wounds

Overall, there is limited, low-quality evidence from 14 peer-reviewed studies suggesting that HBOT may improve healing when employed as an adjunct treatment for venous, arterial, and pressure ulcers, compromised flaps and grafts, and surgical reconstruction (without grafts or flaps). We currently have low confidence in the reported estimate of effects for these conditions and the reported benefits should be interpreted with caution. In addition, there is insufficient evidence from 1 study to determine the effectiveness of HBOT for crush injuries, insufficient evidence (primarily due to mixed results) from 2 studies to determine if HBOT is effective for the treatment of thermal burns, and insufficient evidence from 1 study to determine the effectiveness of HBOT for the treatment of acute traumatic peripheral ischemia.

Table 3. Summary of Evidence by Wound Type for HBOT as a Treatment for Other (Nondiabetic) Nonhealing Wounds

Wound Type	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Venous, arterial, and pressure ulcers	Short-term benefit	2 fair, 2 poor	Low
Compromised grafts and flaps	Benefit	6 poor, 1 unknown	Low
Surgical reconstruction (without grafts or flaps)	Benefit	2 fair	Low
Crush injuries	Mixed	1 fair	Very low
Thermal burns	Mixed	2 fair	Very low
Acute traumatic peripheral ischemia	Benefit	1 poor	Very low

HBOT for Refractory Osteomyelitis

Three systematic reviews (all fair quality) (510 participants) (Lawson, 2003; Goldman, 2009; Hart, 2012), including 23 peer-reviewed studies (0 RCTs, 2 nonrandomized controlled trials, 21 case series), reported on the effectiveness of HBOT for the treatment of refractory osteomyelitis. The outcomes evaluated included resolution/cure, recurrence, and hospital stay.

A systematic review by Hart (2012) was identified in an update search after the initial set of studies had been identified, selected, and abstracted. Hart (2012) included 23 studies (510 participants) (2 prospective cohorts and 21 case series) noting that there are no RCTs evaluating the effectiveness of HBOT for refractory osteomyelitis, and stratified results according to anatomical location (long bone and miscellaneous sites, mandibular, spinal, cranial, malignant external otitis, and sternal). It should be noted that we rated all but two studies included in this review as very poor in quality (in contrast to the author's opinion) due to a high risk of selection bias (see quality assessment section). Furthermore, case series are particularly prone to publication bias usually favoring the intervention under investigation (Albrecht et al., 2009). One fair-quality nonrandomized controlled trial (Barili et al., 2007) was included by Hart and represents the best available evidence. We summarized the findings of the very poor studies under the various outcome sections but recommend substantial caution in interpreting the results as outlined by the author. The other two included systematic reviews (Lawson, 2003; Goldman, 2009) had been selected for inclusion prior to publication of the Hart systematic review, and, although they do not present additional studies, they both report harms data important to the review.

Findings by Outcome

Resolution/cure: All 3 fair-quality systematic reviews reported on this outcome (Lawson, 2003; Goldman, 2009; Hart, 2012). One poor-quality nonrandomized controlled trial (28 participants) was included in all 3 reviews (Esterhai et al., 1987) and suggests no benefit from HBOT as an adjunct treatment to surgery and antibiotics for curing refractory osteomyelitis (HBOT group, 79% [11of 14]; control group, 93% [13 of 14]; P=0.28). In contrast, the median cure rate among the 21 included case series (450 participants) was 87% in favor of HBOT as an adjunct to standard care (range, 37% to 100%).(Hart, 2012).

Relapse: Hart (2012) was the only review to include a fair-quality nonrandomized controlled trial by Barili et al. (2007). This trial was presumed to be excluded from the review by Goldman (2009) because the term osteomyelitis does not appear in the text. This fair-quality trial represents the best-quality available evidence reporting significantly lower infection relapse rates among the HBOT group versus controls (0% versus 33.3%, respectively; *P*=0.024) (Barili et al., 2007). A poor-quality nonrandomized trial by Esterhai et al. (1987) (included in all 3 reviews) found no difference in relapse rates between groups (14% [2 of 14]) in the HBOT group versus 7% [1 of 14] in the control group; *P*=0.54) (Esterhai et al., 1987). Among 5 very-poor-quality case series (74 participants) 4 cases (5.4%) of relapses were reported among patients receiving HBOT (Perrins et al., 1966; Davis et al., 1992; Chen et al., 1998; Chen et al., 2004; Amhed et al., 2009).

Length of hospital stay: One fair-quality nonrandomized controlled trial reported significantly fewer days in the hospital among the HBOT group versus controls (52.6 [SD, 9.1] versus 73.6 [SD, 24.5]; *P*=0.026) (Barili et al., 2007).

Quality Assessment

Systematic Reviews: Applying AMSTAR criteria for rating the quality of systematic reviews, all 3 selected systematic reviews were considered fair quality (Lawson, 2003; Goldman, 2009; Hart, 2012). It should be noted that 2 of the 3 reviews (Goldman, 2009; Hart, 2012) were considered flawed in terms of their assessment of the quality of individual studies but considered sound methodologically in terms of identifying and selecting studies.

Individual Studies: Lawson (2003) applied standard methods to rating the quality of its one included study, and we agreed with the author's assessment. Goldman (2009) employed GRADE criteria as the quality assessment tool, but it is our opinion that the author did not apply the tool effectively, inappropriately rating case series as moderate quality when it is our belief that the appropriate rating should have been poor for the studies in question. Hart (2012) applied the American Heart Association's criteria for assessing the quality of observational studies but, in our assessment, inappropriately rated all 21 included case series as fair quality when they should have been rated very poor. Using this information and applying the Hayes quality checklist system for rating the quality of individual studies, Table 4 provides the results of our quality assessment. We judged the overall quality of individual studies as poor. The most common reasons for assigning a poor-quality rating was the risk of selection bias in observational studies.

Body of Evidence: Based on the results from 23 included primary data studies, Table 4 presents the quality of evidence for the effectiveness of HBOT for the treatment of refractory osteomyelitis. All three included outcomes received a low- or very-low-quality of evidence grade. The overall quality of evidence

was considered low. The high risk of bias associated with the included case series, inconsistency across outcomes, and the risk of publication bias represent the main reasons for the very-low grade assigned.

Summary: Effectiveness of HBOT for refractory osteomyelitis

Low-quality evidence from 23 primary data studies (1 fair quality, 1 poor quality, 21 very poor quality) cannot establish that HBOT is effective as an adjunct treatment for refractory osteomyelitis. There is some evidence from 1 small fair-quality nonrandomized trial that HBOT may reduce the rates of relapse infection but additional, good-quality studies are necessary to confirm this finding.

Table 4. Summary of Evidence by Outcome for HBOT as a Treatment for Refractory Osteomyelitis

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Resolution/cure	Benefit	1 poor, 21 very poor	Very low
Infection relapse rate	Mixed	1 fair, 6 poor	Low
Number of days in the hospital	Benefit	1 fair	Very low

HBOT for Late Radiation Tissue Injury

Four systematic reviews (1 good quality, 3 fair quality) (1628 participants) (Wang et al., 2003; Fritz et al., 2010; Nabil and Samman, 2011; Bennett et al., 2012), including 34 peer-reviewed studies (12 RCTs, 3 prospective cohorts, 6 retrospective cohorts, and 13 case series) plus 1 fair-quality RCT (36 participants) published subsequent to the systematic reviews (Shao et al., 2012), reported on the effectiveness of HBOT for the treatment of LRTI, including osteoradionecrosis (ORN) and soft tissue radionecrosis. Outcomes evaluated included complete resolution or improvement of tissue damage or necrosis; prevention of ORN; late sequelae (LENT-SOMA scores evaluating functional outcomes); QOL; complete mucosal cover for ORN; establishment of bony continuity; healing of tooth sockets; loss of dental implants; and wound dehiscence.

Findings by Indication or Outcome

Complete resolution or improvement of tissue damage or necrosis: Two of the included systematic reviews (Wang et al., 2003; Bennett et al., 2012) plus 1 RCT published subsequently (Shao et al., 2012) reported on this outcome. A complicating factor in the study of HBOT for LRTI is the difficulty in comparing results across anatomical areas. A good-quality Cochrane Review by Bennett et al. (2012) reported pooled data from 4 RCTS, which looked at the complete resolution of tissue damage or necrosis at or before 3 months follow-up across all anatomical areas studied (325 participants) (2 good quality, 1 fair quality, 1 unclear quality due to poor reporting) (Marx, 1999a; Pritchard et al., 2001; Annane et al., 2004; Clarke et al., 2008). Overall, 36% of participants in the HBOT group and 28% in the control group achieved complete resolution. There was, however, significant heterogeneity among the trials, which was not due to sampling variability (I^2=82%) and no overall estimate of effect was provided. In the absence of an overall estimate of effect, the effectiveness of HBOT for the complete resolution of tissue damage for each area studied is provided. A study of indeterminate quality by Marx (1999a) found that complete resolution was significantly higher among patients requiring hemimandibulecotomy and receiving HBOT (RR, 1.4; 95% CI, 1.1-1.8; NNT, 5); a good-quality study by Clarke et al. (2008) found a nonsignificant improvement in the HBOT group toward complete resolution among patients with radiation proctitis (RR, 9.7; 95% CI, 0.6-170.1); a fair-quality study by Annane et al. (2004) found no benefit of HBOT among patients with ORN of the mandible in terms of complete resolution at or before 3 months follow-up (RR, 0.6; 95% CI, 0.25-1.4) (although the validity of the primary outcome in this

study has been questioned); and a good-quality study by Pritchard et al. (2001) reported no resolution in either the HBOT or control groups. In addition, the good-quality trial by Clarke et al. (2008), included previously, combined complete resolution with significant improvement of tissue damage or necrosis and found a significant benefit to HBOT among patients with radiation proctitis (RR, 1.72; 95% CI, 1.0-2.9) (Clarke et al., 2008). A fair-quality RCT, published subsequent to the included systematic reviews (n=16) (Shao et al., 2012), found that HBOT and intravesical hyaluronic acid both aided recovery among patients with radiation induced hemorrhagic cystitis, and reported 75% complete recovery (defined as no symptoms) in the HBOT group at 6 months, 50% at 12 months, and 45% at 18 months (Shao et al., 2012). Finally, a fair-quality 2003 systematic review (Wang et al., 2003), including 13 poor-quality case series (168 participants), all reported a beneficial effect (50% to 100% complete or partial healing) of HBOT on soft tissue radionecrosis (Wang et al., 2003).

Prevention of ORN following tooth extraction in an irradiated field: One good-quality systematic review from the Cochrane Collaboration (Bennett et al., 2009) and two fair-quality systematic reviews (Fritz et al., 2010; Nabil and Samman, 2011) reported on this outcome. All 3 reviews reported just 1 RCT, with an unclear risk of bias due to poor reporting, which found an incidence rate for the development of ORN of 5.4% in the HBOT group versus 29.9% in the control group (RR, 0.18; *P*=0.005) (Marx et al., 1985). Fritz and colleagues and Nabil and colleagues included observational studies in their respective reviews and found similar results from largely the same studies but drew different conclusions from the findings (Fritz et al., 2010; Nabil and Samman, 2011). Nabil and Samman (2011) included 19 studies (1 RCT and 18 observational studies) 8 of which reported on the use of HBOT (433 participants). The authors reported an overall incidence rate of 7% (57 of 828 patients) for ORN among post-radiated head and neck cancer patients but only 4% among patients who received HBOT. They concluded that weak evidence supports the use of HBOT for the prevention of ORN after tooth extraction in irradiated head and neck cancer patients. Fritz et al. (2010) conducted a similar systematic search and included 14 studies (1 RCTs and 13 observational); 7 reported on the use of HBOT, 6 of which had also been included by Nabil and Samman (2011). Fritz and colleagues reported the same overall incidence rates for ORN (7% overall versus 4% for those having undergone HBOT) but concluded that there was insufficient evidence to determine if HBOT was effective in preventing ORN after tooth extraction in irradiated head and neck cancer patients. The 2003 systematic review by Wang and colleagues (described elsewhere) also looked at ORN but does not add anything new to the results provided previously.

Complete mucosal cover and establishment of bony continuity in ORN: A good-quality Cochrane Review by Bennett et al. (2012) pooled data from 3 RCTS (246 participants) (1 fair quality, 2 unclear quality) (Marx et al., 1985; Marx, 1999a; Annane et al., 2004) and reported significant benefit from HBOT in terms of achieving complete mucosal cover among patients with ORN (RR, 1.3; 95% CI, 1.1-1.6; NNT, 5) (Bennett et al., 2012). Also reported in the 2012 Cochrane Review, is a trial by Marx (1999a) reporting significant benefit from HBOT in terms of establishing bony continuity (RR, 1.5; 95% CI, 1.1-1.8).

QOL: The 2012 Cochrane Review (Bennett et al., 2012) included 5 RCTs (287 participants) (2 good quality, 3 fair quality) reporting QOL outcomes, which were not pooled due to significant heterogeneity (Pritchard et al., 2001; Schoen et al., 2007; Clarke et al., 2008; Teguh et al., 2009; Gothard et al., 2010). Among patients with axillary radiation injury, no significant benefit of HBOT was found for general health at 12 months (SF-36® Health Survey [QualityMetric, Inc.], 58.8/100 in HBOT group versus 61.1/100 control group; weighted MD, –2.3; 95% CI, –19 to 14.4) (Pritchard et al., 2001); physical functioning at 12 months (weighted MD, –4.0; 95% CI, –19.4 to 11.4) (Pritchard et al., 2001); or lymphedema-specific functioning (P=NS) (Gothard et al., 2010). A significant benefit of HBOT was found

for improvement in bowel bother subscale among patients with radiation proctitis (pre-post mean improvement 14.1% in HBOT group [P=0.0007] versus 5.8% in control group [P=0.15]) (Clarke et al., 2008); global QOL score among patients with dental implants in irradiated regions (MD, 17.6 points; 95% CI, 2.8-32.2) (Schoen et al., 2007); and 12-month QOL functional outcomes among patients with radiation-related damage following head and neck cancers (improvements included sticky saliva score, P=0.01; dry mouth, P=0.009; and VAS for pain in the mouth, P<0.0001) (Teguh et al., 2009).

Late effects of radiation (LENT-SOMA scores): The 2012 Cochrane Review (Bennett et al., 2012) reported one good-quality RCT (150 participants), which looked at mean improvement in LENT-SOMA scores (an indication of improvement in the late effects of radiation) at completion of treatment and found a significantly greater improvement in the HBOT group (LENT-SOMA score 5.0 of 14 in the HBOT group versus 2.6 of 14 in the control group; MD, 2.4; P=0.002) (Clarke et al., 2008).

Loss of dental implants: One fair-quality trial reported in the 2012 Cochrane Review (Schoen et al., 2007) found that the risk of losing an implanted tooth following implant into an irradiated mandible was 2.5 times greater in the HBOT group versus controls, but this was not statistically significantly (RR, 2.5; *P*=0.22).

Wound dehiscence: A good-quality Cochrane Review by Bennett et al. (2012) pooled data from 2 RCTS (368 participants, with unclear risk of bias due to poor reporting) (Marx, 1999a; Marx, 1999b) and found a significant benefit to HBOT in terms of reducing wound dehiscence (RR, 4.2; 95% CI, 1.1-16.8).

Quality Assessment

Systematic Reviews: Applying AMSTAR criteria for rating the quality of systematic reviews, 1 of 4 selected systematic reviews was considered good quality (Bennett et al., 2012) and 3 were considered fair quality (Wang et al., 2003; Fritz et al., 2010; Nabil and Samman, 2011).

Individual Studies: Each review differed in the approach to rating the quality of individual studies. The review by Bennett et al. (2012) employed the Cochrane Collaboration risk of bias assessment criteria for RCTs, and by our assessment made effective use of the tool. Fritz et al. (2010) effectively assessed the quality of individual studies using well-recognized criteria for quality assessment. Nabil and Samman (2011) did not formally assess the quality of individual studies; however, all but one of the included studies had been quality assessed in the Fritz et al. (2010) review and we had enough information to quality rate the remaining study using Hayes criteria. Wang et al. (2003) made no attempt to rate the quality of individual studies but included 13 case series that we rated poor quality and an RCT that had been quality rated in other reviews. Using this information and applying the Hayes quality checklist system for rating the quality of individual studies, Table 5 provides results of our quality assessment. We rated the overall quality of individual studies as fair. The most common reasons for assigning a poor-quality rating was inadequate randomization, poor or no blinding in RCTs, and the risk of selection bias in observational studies. Three included RCTs, all by the same author (Marx et al., 1985, Marx, 1999a; Marx, 1999b), were rated as unclear risk of bias because the author provided so few details that it precluded reasonable judgment.

Body of Evidence: Based on the results from 35 included primary data studies, Table 5 presents the quality of evidence for the effectiveness of HBOT for the treatment of LRTI. A number of outcomes were judged to have low or very-low-quality evidence, mainly as a result of the paucity of studies, small

sample sizes, indirect evidence, inconsistency across studies, and high risk of bias. Despite this, we judged the overall quality of evidence for the effectiveness of HBOT in the treatment of LRTI to be moderate. Complete resolution or improvement of tissue damage; prevention of ORN following tooth extraction in an irradiated field; and complete mucosal cover and establishment of bony continuity for ORN were considered major outcomes and, therefore, given more weight in our quality assessment process, contributing to the overall moderate quality grade assigned to HBOT for LRTI. Furthermore, most of the outcomes studied found a consistent benefit in favor of HBOT for both ORN and soft tissue radionecrosis and several key fair- and good-quality studies were available.

Summary: Effectiveness of HBOT for LRTI

There is moderate-quality evidence from 35 primary data studies suggesting that HBOT improves outcomes of LRTI affecting bone and soft tissues. There is no overall estimate of effect because of the heterogeneity between studies, but the evidence suggests that radiation-induced tissue and bone damage to the head and neck, anus, and rectum show consistent clinical improvement with HBOT. There is also moderate-quality evidence that HBOT reduces the risk of developing ORN following tooth extraction in a previously irradiated area.

Table 5. Summary of Evidence by Outcome for HBOT as a Treatment for LRTI

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Complete resolution or improvement of tissue damage or necrosis	Benefit	2 good, 2 fair, 14 poor	Moderate
Prevention of osteoradionecrosis (ORN) after tooth extraction	Benefit	1 fair, 7 poor, 1 unclear	Moderate
Complete mucosal cover and establishment of bony continuity for ORN	Benefit	1 fair, 2 unclear	Moderate
QOL	Radiation proctitis: Benefit Radiation injury resulting from head and neck cancers: Benefit Patients with dental implants in irradiated area: Benefit Axillary radiation injury: No benefit	2 good, 3 fair	Moderate
Improvement in late effects of radiation (LENT-SOMA scores)	Benefit	1 good	Low
Loss of dental implants	No benefit	1 fair	Very low
Wound dehiscence	Benefit	2 unclear	Low

HBOT for Brain Injury

Two good-quality systematic reviews (1220 participants) (McDonagh et al., 2003; Bennett et al., 2009), including 16 studies (6 RCTs, 4 uncontrolled pre-post studies, 6 other observational studies) plus one additional fair-quality pre-post study (63 participants) of relevance, but not included in either systematic review, reported on the effectiveness of HBOT for the treatment of brain injury, including traumatic and other brain injuries. The outcomes evaluated included mortality and functional outcomes.

Findings by Indication and Outcome

Mortality among TBI patients: A good-quality Cochrane Review by Bennett and colleagues pooled data from 4 fair-quality trials (387 TBI patients) (Holbach et al., 1974; Artru et al., 1976a; Rockwold et al.,

1992; Xie and Li, 2007) and reported a significantly reduced risk of dying among those receiving HBOT compared with controls (RR, 0.69; 95% CI, 0.54-0.88). The absolute difference was significant at 15%, and the number needed to treat (NNT) to avoid 1 death was 7 (95% CI, 4-22) (Bennett et al., 2009). The number of HBOT sessions varied from 10 to 40. Enrolment into the study following hospital admission varied across the studies. Rockswold (1992) reported enrollment after 6 hours; Xie (2007) reported enrollment after 24 hours; Artru (1976) reported enrollment after 4.5 days, and Holbach (1974) did not specify any period before entry into the study.

Functional outcomes among TBI patients: Bennett and colleagues pooled data from 2 fair-quality trials (159 TBI patients) (Holbach et al., 1974; Artru et al., 1976a) and found no statistically significant reduction in the proportion of TBI patients with unfavorable functional outcomes at the end of HBOT treatment to 4 weeks follow-up (RR, 0.38; 95% CI, 0.10-1.37). However the absolute risk difference between HBOT and sham treatment groups was significant (*P*=0.04) at 22.3% with the NNT to achieve 1 additional good outcome equal to 4 (95% CI, 3-11) (Bennett et al., 2009). At 6 months follow-up, Bennett and colleagues found one poor-quality trial (Ren et al., 2001) (55 TBI patients) reporting a significant reduction in the risk of an unfavorable functional outcome following HBOT (RR, 0.36; 95% CI, 0.18-0.72), an absolute risk difference between the HBOT and sham treatment groups of 22.3% (*P*=0.04), and the NNT for 1 additional good outcome of 4 (95% CI, 3-11) (Bennett et al., 2009). At 1-year follow-up, Bennett and colleagues found one fair-quality trial (Rockswold et al., 1992) (168 TBI patients), which found no statistical reduction in the risk of an unfavorable outcome following HBOT (RR, 1.02; 95% CI, 0.77-1.36). In addition, Bennett and colleagues pooled the results from all 4 trials (382 TBI patients) (Holbach et al., 1974; Artru et al., 1976a; Rockswold et al., 1992; Ren et al., 2001) to determine if HBOT reduced the risk of an unfavorable functional outcome at any final assessment point and found no significant reduction in the risk of an unfavorable outcome following HBOT (RR, 0.51; 95% CI, 0.25-1.08) (Bennett et al., 2009). It should be noted that there was significant heterogeneity between the trials (I^2=81%) and the results were borderline sensitive to the number of dropouts in one of the trials. In the best case scenario, the absolute risk difference between the HBOT and sham treatment groups was significant at 18% (*P*=NR). The NNT to avoid 1 poor outcome was 6 (95% CI, 4-12) (Bennett et al., 2009). A good-quality Agency for Healthcare Research and Quality (AHRQ) systematic review by McDonagh et al. (2003) included 3 of the RCTs and discussed the results for the Bennett et al. (2009) review. In addition, McDonagh and colleagues looked at observational data and in a poor-quality pre-post study of just 6 TBI patients reported poor functional outcomes among all survivors (Artru et al., 1976b). McDonagh et al. (2003) reported on 4 other observational studies, all of which reported on physiological outcomes (such as intracranial pressure and cerebrospinal pressure) rather than patient-important outcomes and are therefore not described here.

Mortality among patients with non-TBI brain injury: McDonagh et al. (2003) reported 1 poor-quality pre-post study (136 patients) (Mathieu et al., 1987), which found 7% mortality among patients following HBOT.

Functional outcomes among patient with non-TBI brain injury: McDonagh et al. (2003) found one poor-quality uncontrolled observational study (32 patients) reporting a 5% to 10% improvement in memory (Bender-Gestalt memory test and 7 unvalidated measures were used to create a memory score) among patients having undergone HBOT (Imai et al., 1974). A poor-quality pre-post test study (with historical controls) published subsequent to the 2003 AHRQ review found that patients with chronic brain injury (including cerebral palsy, stroke, TBI, anoxic ischemic encephalopathy, and Lyme disease) had significantly improved cognitive performance following HBOT when compared with brain injured or

normal controls (Golden et al., 2006). The overall mean change in cognitive performance among children receiving HBOT was 43.57 (SD, 31.45) versus 3.71 (SD, 5.99) among brain-injured controls and 21.33 (SD, 7.81) among normal controls (*P*=0.000). Similarly, the overall mean change in cognitive performance among adults receiving HBOT was significantly better than controls with mean change in cognitive performance 62.73 (SD, 42.01) among the HBOT group, 1.13 (SD, 13.27) among brain-injured controls, and 8.10 (SD, 6.69) among normal controls (*P*<0.01) (Golden et al., 2006). We have very low confidence in the reliability of these results, particularly since the treatment group showed significantly poorer cognitive performance pre-test than did the brain-injured controls, increasing the likelihood for selection bias. Furthermore, the authors gave no explanation for the significant pre-post test difference observed among the normal controls.

Symptoms among patients with non-TBI brain injury: McDonagh et al. (2003) included 1 poor-quality RCT (92 patients), which reported a significantly higher proportion of patients cured in the HBOT group compared with controls (38% [18 of 47] versus 18% [8 of 45]; *P*<0.05) (Jianhua et al., 1995) and a very poor-quality case series that reported a cure rate of 68% (65 of 95) following HBOT among patents in a coma for a variety of etiologies (Shn-rong, 1995). There were several methodological flaws in these studies, and we have very-low confidence in the reliability of the results. McDonagh et al. (2003) also reported a very-poor-quality uncontrolled observational study (10 patients) reporting a 40% (4 of 10) improvement in symptoms among children with radiation-induced necrosis of the central nervous system (Chuba et al., 1997).

Quality Assessment

Systematic Reviews: Applying AMSTAR criteria for rating the quality of systematic reviews, both included systematic reviews (McDonagh et al., 2003; Bennett et al., 2009) were considered good quality.

Individual Studies: Each review differed in the approach to rating the quality of individual studies. The review by Bennett et al. (2009) employed the Cochrane Collaboration risk of bias assessment criteria for RCTs, and by our assessment made effective use of the tool. McDonagh et al. (2003) employed standard AHRQ methods to rate the quality of individual studies applying the methods effectively. Using this information and applying the Hayes quality checklist system for rating the quality of all of the individual studies, Table 6 provides the results of our quality assessment. We rated the overall quality of individual studies as fair for TBI and poor for other brain injuries. The most common reasons for assigning a poor-quality rating was inadequate randomization, poor or no blinding in RCTs, and the risk of selection bias in observational studies.

Body of Evidence: Based on the results from 16 included primary data studies, Table 6 presents the quality of evidence for the effectiveness of HBOT for the treatment of brain injury (TBI and other brain injuries). We judged the overall quality of the evidence for TBI as moderate mainly due to the availability of 4 fair-quality trials and general consistency in the results. On the other hand, we found very-low-quality studies, inconsistent findings, and poor precision in the studies looking at non-TBI brain injuries and, consequently, judged the overall quality of the evidence for outcomes related to non-TBI brain injuries as very low.

Summary: Effectiveness of HBOT for brain injuries

Moderate-quality evidence from 10 primary data studies suggests that although HBOT may reduce the risk of dying following a TBI,there is little evidence that those who survive have a good functional outcome. Based on the available data, the review authors did not recommended routine application of HBOT to TBI patients

Evidence from 6 poor-quality primary data studies is insufficient to determine if HBOT is effective in improving health outcomes among patients with brain injuries other than TBI.

Table 6. Summary of Evidence by Outcome for HBOT as a Treatment for Brain Injury

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Mortality among patients with traumatic brain injury (TBI)	Benefit (i.e. reduced risk of dying but with no evidence of improved function upon survival)	4 fair	Moderate
Functional outcomes among patients with TBI	No benefit	3 fair, 2 poor	Moderate
Mortality among patients with non-TBI brain injuries	Unknown benefit	1 poor	Very low
Functional outcomes among non-TBI brain injury patients	Benefit	2 poor	Very low
Symptoms among non-TBI brain injury patients	Benefit	1 poor, 2 very poor	Very low

HBOT for Cerebral Palsy

One systematic review (449 participants), including 6 studies (2 RCTs, 4 observational studies) (449 participants), reported on the effectiveness of HBOT for the treatment of cerebral palsy (McDonagh et al., 2007). This review was an update of a 2003 AHRQ report by the same author. The outcomes evaluated included motor function (change in gross motor function measure [GMFM]) and percentage of improvement in GMFM; caregiver assessment (using the Pediatric Evaluation of Disability Inventory [PEDI] scale); and other disease-specific outcomes such as improvement in speech, social functioning, and cognitive ability.

Findings by Outcome

Motor function: One fair-quality RCT (Collet et al., 2001) and 2 fair-quality observational studies (rated fair by the author of the review) (Montgomery et al., 1999; Waalkes et al., 2002) reported on motor function. Collet and colleagues found a statistically and clinically significant improvement in both the HBOT and control groups immediately following 40 HBOT treatments and again at 6 months follow-up (mean change in GMFM immediately posttreatment was 2.9 in the HBOT group versus 3.0 in the control group, *P*=NS; mean change at 6 months follow-up was 3.4 in the HBOT group versus 3.1 in the control group, *P*=NS) (Collet et al., 2001). It should be noted that the control group received air pressurized to 1.3 atmosphere absolute (ATA), which may explain the improvement seen among control participants and the lack of difference between the groups. Montgomery et al. (1999), in a fair-quality prospective pre-post test study, reported a 5.3% improvement in GMFM scale among 25 patients receiving 20 sessions of HBOT at 1.75 ATA, and Waalkes et al. (2002), in a small but fair-quality prospective pre-post test study, reported an 8.9% improvement in GMFM scale among 7 patients receiving 40 sessions of

HBOT at 1.7 ATA. The differences in baseline GMFM and number of treatment sessions make it difficult to compare the results of these 3 studies.

Caregiver assessment (PEDI scale): Two RCTs reported on this outcome (Packard, 2000; Collet et al., 2001). One fair-quality RCT found that the control group had significantly better mobility and social functioning posttreatment (results NR) (Collet et al., 2001). A poor-quality RCT reported no difference between groups in PEDI scores according to the results from blinded assessors (results NR) but found a significant improvement in PEDI mobility subscore favoring HBOT among unblinded parents (results NR) (Packard, 2000). These results should be considered unreliable due to a complete lack of reporting on important study characteristics in the Packard study.

Other disease-specific outcomes: Chavdarov (2002) reported improvements of 13% for motor function, 6% for cognitive abilities, and 7% for speech abilities 2 days post HBOT in a poor-quality prospective time-series of 50 patients. Baseline data were not presented, making it difficult to generalize these results to other children with cerebral palsy (Chavdarov, 2002). One other poor-quality retrospective time-series (230 participants) reported 95% reduced spasticity immediately post HBOT, which persisted among 76% of 82 children at 6 months follow-up (Machado, 1989). High risk of bias makes these results particularly unreliable.

Quality Assessment

Systematic Reviews: Applying AMSTAR criteria for rating the quality of systematic reviews, we assessed the included systematic review as good quality

Individual Studies: McDonagh et al. (2007) employed standard AHRQ methods to rate the quality of individual studies, applying the methods effectively. Applying the Hayes quality checklist system for rating the quality of individual studies, Table 7 provides the results of the quality assessment. Overall, we rated the quality of individual studies as fair for the outcome of motor function but poor for all other outcomes.

Body of Evidence: Table 7 presents the results for the quality of the evidence in relation to the effectiveness of HBOT for the treatment of cerebral palsy. The overall quality of the body of evidence was judged as low for motor function, despite an overall rating of fair for the quality of individual studies. Inconsistencies in the direction of results, a paucity of studies, small sample sizes, differences in baseline characteristics, and the number of treatment sessions provided, all contributed to the low-quality of evidence grade. The overall quality of the evidence for all other outcomes was considered very low.

Summary: Effectiveness of HBOT for cerebral palsy

There is insufficient evidence from 6 studies (2 RCTS and 4 observational studies) to determine the effectiveness of HBOT for the treatment of cerebral palsy. Observational data of fair to poor quality suggests an improvement in motor function and other disease-specific subjective outcome measures among children receiving HBOT, but a fair-quality RCT found no additional benefit from HBOT among children receiving HBOT versus those receiving pressurized air.

Table 7. Summary of Evidence by Outcome for HBOT as a Treatment for Cerebral Palsy

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Motor function	Mixed (1 showed no benefit, 2 showed benefit)	3 fair	Low
Caregiver/Pediatric Evaluation of Disability Inventory (PEDI)	Benefit	1 fair, 1 poor	Low
Other disease-specific outcomes	Benefit	2 poor	Very low

HBOT for Multiple Sclerosis

One systematic review, including 9 RCTs (10 publications) (504 participants), reported on the effectiveness of HBOT for the treatment of multiple sclerosis (MS) (Bennett and Heard, 2011). The primary outcomes evaluated included objective assessments of improvement in MS by a neurologist/hyperbaric physician (Kurtzke Expanded Disability Status Scale [EDSS]) and the number of patients suffering disease exacerbations; secondary outcomes included global and individual Functional Status Scores (FSS) assessed by a neurologist as well as those reported by the patient.

Findings by Outcome

Reduction in EDSS: The pooled results from 5 trials (271 participants) (Fischer et al., 1983; Neiman et al., 1985; Harpur et al., 1986; Wiles et al., 1986; Oriani et al., 1990b) assessing the effectiveness of HBOT immediately following 20 treatment sessions demonstrated no significant reduction in the mean EDSS with HBOT versus sham treatment (mean change with HBOT versus sham treatment, 0.07; 95% CI, –0.23 to 0.09). Pooled 6-month results from 3 trials (163 participants) (Fischer et al., 1983; Harpur et al., 1986; Oriani et al., 1990b) also demonstrated no significant reduction in the mean EDSS in the HBOT group versus the sham treatment group (mean change with HBOT versus sham treatment, –0.22; 95% CI, –0.54 to 0.09). Two trials (81 participants) were pooled to examine the outcome at 1-year posttreatment (Fischer et al., 1983; Oriani et al., 1990b) and found a significant reduction in mean EDSS among those receiving HBOT versus sham treatment (mean change, –0.85; 95% CI, –1.28 to –0.42). It should be noted, however, that the 2 trials available for pooling at 12 months were the only 2 trials to report a benefit from HBOT among the 9 included RCTs.

Prevention of exacerbation: HBOT was not found to reduce the chance of having an exacerbation in any of the 5 studies reporting on the outcome. One fair-quality trial (117 participants) found no difference in the odds of having an exacerbation between patients receiving HBOT and those receiving a sham treatment during 1 month of treatment (OR, 0.31; 95% CI, 0.01-7.8) (Barnes et al., 1985). Similarly, 2 fair-quality trials (122 participants) (Harpur et al., 1986; L'Hermitte et al., 1986) were pooled to determine if HBOT reduced disease exacerbations in the 6 months posttreatment period and also found no significant difference between groups (OR, 0.74; 95% CI, 0.25-2.22). Furthermore, 2 trials (153 participants) looked at the same outcome throughout 1-year follow-up (Fischer et al., 1983; Barnes et al., 1987) and reported no reduction in the odds of exacerbation among patients receiving HBOT (OR, 0.38; 95% CI, 0.04-3.22; P=0.4).

FSS: Four studies were pooled to determine if HBOT improved global FSS scores at the end of 20 treatment sessions (Neiman et al., 1985; Harpur et al., 1986; L'Hermitte et al., 1986; Oriani et al., 1990b) (194 participants). The results showed no significant difference between groups (29% improvement in the HBOT group versus 28% in the sham group) (OR, 1.17; 95% CI, 0.59-2.33). Similarly, 7 of 9 included

trials reported no significant difference between HBOT and sham treatment in terms of individual FSS elements. Two pooled trials (Barnes et al., 1987; Oriani et al., 1990b) did find that 10 patients (11%) had improved pyramidal function at 6 months posttreatment in the HBOT group versus 2 (2.3%) in the sham group (odds of failing to improve: OR, 0.17; 95% CI, 0.07-0.78; NNT, 11; 95% CI, 6-63). In addition, Oriani et al. (1990b) found that 12 patients (13.2%) showed improved pyramidal function 12 months posttreatment in the HBOT group versus 4 (4.5%) in the sham group (odds of failing to improve: OR, 0.13; 95% CI, 0.03-0.58; NNT, 11; 95% CI, 6-197).

Quality Assessment

Systematic Reviews: Applying AMSTAR criteria for rating the quality of systematic reviews, we assessed the included systematic review as good quality (Bennett and Heard, 2011).

Individual Studies: The review by Bennett and Heard (2011) employed the Cochrane Collaborations well-recognized risk of bias assessment criteria for RCTs, and by our assessment made effective use of the tool. Applying the Hayes quality checklist system for rating the quality of individual studies, Table 8 provides the results of the quality assessment.

Body of Evidence: Table 8 presents the results for the quality of the evidence related to the effectiveness of HBOT for the treatment of MS. Taking into consideration individual study quality, consistency, directness, applicability, and the risk of publication bias, we judged the body of evidence for each outcome of interest as moderate.

Summary: Effectiveness of HBOT for multiple sclerosis

Moderate-quality evidence from 9 trials suggests little effect of HBOT on outcomes related to MS. Two small, good-quality trials found modest benefits, while 7 fair-quality trials found no benefit. Furthermore, the statistical benefits observed in the 2 positive trials are unlikely to translate into clinically significant benefits for the patient. Of note, there were no RCTs found on this topic post 1990, and there appears to be little interest in further investigation into the use of HBOT for MS.

Table 8. Summary of Evidence by Outcome for HBOT as a Treatment for Multiple Sclerosis

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Reduction in Expanded Disability Status Scale (EDSS)	0 and 6 months f/u (n=7 studies): No benefit 12 month f/u (n=2 studies): Benefit	2 good, 3 fair	Moderate
Prevention of exacerbation	No benefit	1 good, 4 fair	Moderate
Functional Status Score (FSS)	Global FS: No benefit Individual FSS: No benefit Pyramidal FS: Benefit	2 good, 7 fair	Moderate

HBOT for Migraines and Cluster Headaches

One systematic review (119 participants), including 7 RCTs, reported on the effectiveness of HBOT for the treatment and prevention of cluster headaches or migraines (Bennett et al., 2008). Five of the 7 trials evaluated HBOT for migraines (Fife et al., 1992; Hill, 1992; Myers and Myers, 1995; Wilson et al., 1998; Eftedal et al., 2004), and 2 looked at cluster headaches (Di Sabato et al., 1993; Nilsson Remahl et

al., 2002). The outcomes evaluated included relief from migraine/headache, requirement for rescue medication, pain intensity, number of headache days per week, sustained relief, and headache index.

Findings by Outcome

Migraine relief: Bennett and colleagues pooled 3 fair-quality trials (43 participants) and found a significant positive effect on relief from acute migraines following 40 to 45 minutes of HBOT (RR, 5.97; 95% CI, 1.46-24.38; NNT, 2; 95% CI, 1-2) (Fife et al., 1992; Hill, 1992; Myers and Myers, 1995) The authors determined that > 70% of sufferers will obtain relief with the NNT of 2 (95% CI, 1-2) compared with a sham treatment.

Migraine patients requiring rescue medication or experiencing a reduction in nausea and vomiting: Bennett et al. (2008) reported 1 fair-quality trial (40 participants) that found no significant difference in the percentage of patients requiring rescue medication in the first week after receiving HBOT versus a sham treatment (RR, 0.84; 95% CI, 0.64-1.11) (Eftedal et al., 2004) nor in the percentage of patients experiencing nausea with or without vomiting in the first week after receiving HBOT versus a sham treatment (RR, 1.27; 95% CI, 0.68-2.38) (Eftedal et al., 2004).

Pain intensity and frequency of headaches among migraine patients: One fair-quality trial reported no difference between groups in mean pain intensity score immediately posttreatment among 8 patients enrolled in a crossover trial (MD, 2.8; 95% CI, –4.69 to 10.29) (Wilson et al., 1998). Another fair-quality trial reported no differences between groups in the mean number of headache days per week during 1-, 4-, or 8-weeks posttreatment (MD during week 1, –0.13; 95% CI, –1.41 to 1.15; MD during week 4, –0.25; 95% CI, –1.52 to 1.02; MD during week 8, –0.75; 95% CI, –2.06 to 0.56) (Eftedal et al., 2004).

Cluster headache relief: One small, poor-quality trial (13 participants) found that more patients experienced relief from cluster headaches within 20 minutes of receiving HBOT (6 of 7 patients) than those that did not receive HBOT (0 of 6 patients) but the result was not significant (RR, 11.38; 95% CI, 0.77-167.85) (Di Sabato et al., 1993). The study found that 86% of the HBOT group obtained relief and sustained it for 48 hours versus none in the sham group, but the study did not have the power to find the effect significant.

Headache index: Nilsson Remahl et al. (2002) conducted a small crossover trial of fair quality involving 16 patients to investigate the effectiveness of HBOT for treating cluster headaches. The headache index was determined over the period of 1 week and success was defined as a 50% reduction in the headache index during the week following treatment. HBOT offered no benefit in reducing the headache index over the control (RR, 0.98; 95% CI, 0.40-2.41) (Nilsson Ramahl et al., 2002).

Quality Assessment

Systematic Reviews: Applying AMSTAR criteria for rating the quality of systematic reviews, we assessed the included systematic review as good quality

Individual Studies: The review by Bennett et al. (2008) employed the Cochrane Collaborations well-recognized risk of bias assessment criteria for RCTs, and by our assessment made effective use of the tool. Applying the Hayes quality checklist system for rating the quality of individual studies, Table 9 provides the results of the quality assessment

Body of Evidence: Table 9 presents the results for the quality of the evidence in relation to the effectiveness of HBOT for the treatment and prevention of migraines and cluster headaches. The overall quality of the body of evidence was judged as moderate for the effectiveness of HBOT to relieve migraines. Three trials were suitable for pooling of data providing a moderately reliable estimate of effect. The overall quality of the body of evidence for the use of HBOT for treating or preventing cluster headache is very low. There is insufficient evidence from the available trials to determine the effectiveness of HBOT. The trials were small and underpowered and had a significant risk of bias.

Summary: Effectiveness of HBOT for migraines and cluster headaches

Moderate-quality evidence from 3 fair-quality RCTs suggests that 40 to 45 minutes of HBOT is effective in significantly relieving an acute migraine attack. The NNT is 2 patients to obtain significant relief for 1 additional patient. There is no evidence that HBOT can prevent migraines, reduce the nausea and vomiting associated with migraines, or to reduce the need for rescue medication. There is insufficient evidence from 2 studies to determine the effectiveness of HBOT for preventing, relieving, or terminating cluster headaches.

Table 9. Summary of Evidence by Outcome for HBOT as a Treatment or Prevention for Migraines and Cluster Headaches

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Migraine relief	Benefit	3 fair	Moderate
Reduction in nausea and vomiting	No benefit	1 fair	Very low
Need for rescue medication	No benefit	1 fair	Very low
Migraine pain intensity	No benefit	1 fair	Very low
Frequency of migraines	No benefit	1 fair	Very low
Relief from cluster headaches	No benefit	1 poor	Very low
Headache index	No benefit	1 fair	Very low

HBOT for Sensorineural Hearing Loss

One good-quality systematic review from the Cochrane Collaboration originally published in 2007 and updated in 2009 (Bennett et al., 2007), including 7 RCTs (396 participants) (Pilgramm et al., 1985; Hoffman et al., 1995a; Hoffman et al.,1995b; Cavallazzi et al., 1996; Schwab et al., 1998; Fattori et al., 2001; Topuz et al., 2004) plus 1 fair-quality RCT (57 participants) published since the release of the systematic review (Cekin et al., 2009), reported on the effectiveness of HBOT as a treatment for sensorineural hearing loss. The studies can be divided into those that looked at HBOT in the acute or chronic phases following the onset of hearing loss. The primary outcome across studies was improvement or return of hearing. A number of subgroup analyses were conducted among the included studies, the details of which are discussed under KQ3.

Findings by Phase

Acute phase: All 7 RCTs included in the 2007 Cochrane Review looked at pure tone audiometric (PTA) change in hearing following HBOT during the acute phase of sensorineural hearing loss. Three measured the proportion of patients who achieved hearing improvement as a result of HBOT, and 4 measured absolute mean improvement. Bennett et al. (2007) pooled data from 2 trials (114 participants) (1 fair quality 1 poor quality) and found a significant improvement in the proportion of patients with > 25%

return of hearing at the end of HBOT versus control (RR, 1.39; 95% CI, 1.05-1.84; NNT, 5; 95% CI, 3-20) but no significant improvement in the proportion of patients with > 50% return of hearing (RR, 1.53; 95% CI, 0.85-2.78) (Cavallazzi et al., 1996; Fattori et al., 2001). One fair-quality trial (50 participants) included in the review found that patients receiving HBOT had a significantly better improvement in PTA from baseline to posttreatment than did controls (61% versus 24%, respectively) (weighted MD, 37% in favor of HBOT; 95% CI, 22%-53%) (Fattori et al., 2001). Of 4 trials that looked at mean improvement in hearing (across all frequencies), data could be pooled from just 2 studies (1 fair quality 1 poor quality) (Pilgramm et al., 1985; Topuz et al., 2004), and the results indicate that there was a significant improvement with HBOT versus controls (MD 15dB greater with HBOT; 95% CI, 1.5-29.8). However, Bennett and colleagues reported one fair-quality trial (20 participants) that found no significant improvement between groups in the absolute improvement in PTA > 20dB (RR for absolute improvement with HBOT, 3.0; 95% CI, 0.14-65.9) (Hoffman et al., 1995b).

Since publication of the 2007 Cochrane Review, Cekin et al. (2009), in a fair-quality RCT involving 57 patients, found no significant benefit to HBOT in addition to steroids versus steroids alone for the treatment of sudden sensorineural hearing loss (SSHL) in the acute phase (78.95% complete or moderate recovery among the HBOT group versus 71.3% complete or moderate recovery among the control group; *P*=NS). Whether or not there is a difference in the effectiveness of HBOT if used as the primary treatment for SSHL as an adjunct to other treatments (such as steroids and vasodilators) or as a secondary treatment following failure of other treatments has not been directly investigated. We noted that the results outlined by Bennett et al. (2007) appeared to favor HBOT as an adjunct to other treatments rather than as primary treatment, but this observation was not analyzed by the authors, is not supported by the recent trial by Cekin et al. (2009), and cannot be confirmed by this report.

Chronic phase: In relation to the effectiveness of HBOT for the treatment of chronic sensorineural hearing loss, the 2007 Cochrane Review reported 1 fair-quality trial showing no significant difference between groups in the proportion of patients with improvement in PTA (RR for improvement with HBOT, 0.64; 95% CI, 0.30-1.33) (Hoffman et al., 1995a) and 1 fair-quality study showing no significant mean improvement in hearing across all frequencies (MD 1.4 dB in favor of HBOT group; 95% CI, –3.2 to 6.0) (Pilgramm et al., 1985).

Quality Assessment

Systematic Reviews: Applying AMSTAR criteria for rating the quality of systematic reviews, we assessed the included systematic review as good quality

Individual Studies: The review by Bennett et al. (2007) employed the Cochrane Collaborations well-recognized risk of bias assessment criteria for RCTs, and by our assessment made effective use of the tool. Applying the Hayes quality checklist system for rating the quality of individual studies, Table 10 provides the results of the quality assessment. We employed the Hayes checklist tool to assess the quality of the primary study published subsequent to the systematic review and rated it fair quality in terms of internal validity.

Body of Evidence: Table 10 presents the results for the quality of evidence in relation to the effectiveness of HBOT for the treatment of sensorineural hearing loss. The overall quality of the body of evidence was judged as low for the acute phase of hearing loss and moderate for the chronic phase. Some of the included studies looking at the acute phase of hearing loss were problematic in terms of

poor reporting and small sample sizes. Furthermore, there was inconsistency in the direction of the results, and the likelihood of spontaneous recovery irrespective of treatment made it difficult to confirm a benefit to HBOT. The studies that looked at the chronic phase of the disease were consistent in their findings.

Summary: Effectiveness of HBOT for sensorineural hearing loss

Low-quality evidence (due to mixed results) from 8 RCTs is inconclusive as to whether there is a benefit of HBOT for the treatment of sensorineural hearing loss in the acute phase of the disease. A large systematic review suggests that HBOT is beneficial among patients who present within 2 weeks of onset; however, there is no evidence that the statistical benefit observed translates into a functional benefit, and results from a recent RCT does not support that finding. Moderate-quality evidence suggests that HBOT provides no added benefit to patients presenting with chronic sensorineural hearing loss.

Table 10. Summary of Evidence by Outcome for HBOT as a Treatment for Sensorineural Hearing Loss

Outcome	Direction of Effect	Quality of Individual Studies	Quality of Evidence
Hearing improvement/recovery in acute sensorineural hearing loss	Mixed	4 poor, 4 fair	Low
Hearing improvement/recovery in chronic sensorineural hearing loss	No benefit	2 fair	Moderate

Key Question #1a: What is the optimal frequency, dose, and duration of HBOT treatment?

Findings

Frequency of HBOT sessions: No study looked directly at the optimal frequency for HBOT, but 2 systematic reviews (Bennett and Heard, 2011; Kranke et al., 2012).and 1 case series (Muzzi et al., 2010) conducted subgroup analysis examining whether the number of HBOT sessions influences the effectiveness of treatment. Kranke et al. (2012) pooled data from 5 RCTs (Doctor et al., 1992; Faglia et al., 1996; Abidia et al., 2003; Duzgun et al., 2008; Löndahl et al., 2010) (1 good quality, 1 fair quality and 3 poor quality) and found that the observed effect of no significant benefit to HBOT for reducing the rate of major amputation among patients with diabetic foot ulcers was true for both a short course of HBOT (< 30 treatment sessions) (RR, 0.29; 95% CI, 0.07-1.16) or a longer course (> 30 sessions) (RR, 0.40; CI, 0.07-2.23). Of note, the results included a trial, which excluded patients with a high risk for major amputation and should therefore be interpreted cautiously (Kranke et al., 2012). Bennett and Heard (2011) also conducted a subgroup analysis with respect to treatment length (20 sessions versus 20 sessions plus "top-ups") in a systematic review examining the effects of HBOT on MS and found conflicting results from 2 good-quality trials that looked at treatment session number. Fisher et al. (1983) found that there was a significant benefit of HBOT in terms of mean EDSS improvement at 6 months for those having a shorter course of treatment (20 sessions versus 20 sessions plus 5 months of boosters) (shorter course difference in mean change in HBOT group versus sham, –0.84; 95% CI, –1.43 to –0.25; longer course difference in mean change in HBOT group versus sham, –0.29; 95% CI, –0.91 to 0.33). Conversely, Oriani et al. (1990a) found a significant benefit of HBOT for those having a longer course of treatment but not for the shorter course (20 sessions versus > 20 sessions) (longer course, OR, 0.19; 95% CI, 0.05-0.73; shorter course, OR, 0.34; 95% CI, 0.01-8.64). The heterogeneity between trials could not be explained by looking at dose or differences in the control groups. In a poor-quality case

series of 19 patients, Muzzi and colleagues (2010) found no differences in hearing improvement based on number of treatment sessions (> 30 sessions versus < 30 sessions) or if treatment was provided within 15 days of presentation versus 15 to 30 days. Surprisingly, the patients appeared to improve more if treatment was delayed 30 days (Muzzi et al., 2010).

Duration of treatment sessions: No studies examined the duration of treatment sessions. Among the included studies, the duration of treatment for many indications was most often between 60 to 90 minutes per session, with the exception of cluster headaches, where the typical duration of treatment was a 30- to 60-minute session.

Dose: A lack of data precluded many of the included systematic reviews from investigating the optimal dose for effective HBOT. For example, Villanueva et al. (2004) planned to look at oxygen dose among patients receiving HBOT as an adjunct treatment for thermal burns, but found that a subgroup analysis was not possible because of the paucity of studies. Bennett and colleagues looked at HBOT for the treatment of TBI and conducted a subgroup analysis (including 4 RCTs; 3 fair quality, 1 poor quality) by treatment pressure and found that the application of high treatment pressure (2.5 ATA) was associated with a better outcome than lower treatment pressure (1.5 ATA) (unfavorable functional outcome at 2.5 ATA: RR, 0.48; 95% CI, 0.27-0.87; *P*=0.01; unfavorable outcome at 1.5 ATA: RR, 0.47; 95% CI, 0.08-2.85; *P*=0.41) (Bennett et al., 2009). Meanwhile, 1 fair-quality trial from another Cochrane Review investigating the effectiveness of HBOT for the treatment and prevention of migraines and cluster headaches found that HBOT was no more effective than air in relieving acute migraines (RR, 6.23; 95% CI, 0.47-82.92; *P*=0.17) but better than normobaric oxygen (RR, 9.0; 95% CI, 1.39-58.44; *P*=0.02) (Myers et al., 1995).

Quality Assessment

Table 11 summarizes the results and quality assessment for KQ1a. Three good-quality systematic reviews conducted some form of subgroup analyses relevant to the question of frequency and dose but none looked at the duration of treatment sessions. We rated the quality of individual studies as fair for frequency and dose but judged the overall quality of the body of evidence as low.

Summary: Optimal frequency, dose, and duration of HBOT treatment

The available data from 13 studies provides insufficient evidence to determine the optimal treatment frequency, duration, or dose for HBOT. No studies reported on the optimal duration of treatment sessions; there were mixed results from subgroup analysis involving 8 studies looking at frequency; and significant heterogeneity means that we have low confidence in the available results from 5 studies, which looked at dose.

Table 11. Summary of the Evidence Related to the Frequency, Duration, or Dose of HBOT

	Frequency of HBOT Sessions	Duration of Treatment Sessions	Dose
Range across studies	1-101	20-120 minutes	1.0-3.0 atmospheres absolute (ATA)
Findings from subgroup analyses	No difference between a longer treatment course (>30 sessions) and a shorter course (<30 sessions) among patients with diabetic foot ulcers or sensorineural hearing loss; conflicting results for patients with multiple sclerosis	None	Oxygen dose of 2.5 ATA was more effective than 1.5 ATA for patients with traumatic brain injury (TBI) but the heterogeneity between studies was very high
Optimal	Unable to determine	Unable to determine	Unable to determine
Overall quality of individual studies	Fair	Not available (NA)	Fair
Quality of the body of evidence	Low	NA	Low

Key Question #2: What harms are associated with HBOT?

Findings

Several of the systematic reviews selected to answer KQ1 reported harms data, some planned to look at harms-specific outcomes a priori, others reported adverse events more incidentally Three systematic reviews, not included in KQ1, contributed additional harms data (MSAC, 2003; Garcia-Corrubias et al, 2005; Weaver, 2011). In all, 15 systematic reviews provided data on the safety of HBOT for the indications under investigation. We also included data from 4 primary data studies obtained through a search of the literature for harms-specific studies (Al-Waili et al., 2006; Muller-Bolla et al., 2006; Toklu et al., 2008; Rockswold et al., 2010) as well as harms data from 6 related Hayes technology assessment (HTA) reports on the topic (Hayes, Inc., 2007; Hayes, Inc., 2008a; Hayes, Inc., 2008b; Hayes, Inc., 2009b; Hayes, Inc., 2010; Hayes, Inc., 2011). Some of the included systematic reviews and primary data studies looked at harms associated with HBOT for specific indications; others combined indications, and some discussed issues related to the safe provision of HBOT as it relates to staffing and facilities. The results outlined below begin with general harms followed by the harms reported among studies of populations with specific indications. The summary synthesizes the overall risks across populations.

General Safety: Four HTAs and 2 health technology briefs (HTBs), conducted by Hayes Inc., reported on the general safety of HBOT (Hayes, Inc., 2007; Hayes, Inc., 2008a; Hayes, Inc., 2008b; Hayes, Inc., 2009; Hayes, Inc., 2010; Hayes, Inc., 2011).

The evidence suggests that harms associated with HBOT are generally mild and self-limiting. The majority of the reported harms include barotrauma, temporary visual disturbances, and, more rarely, oxygen toxicity. Occasional reports of seizures represent the most serious side effects. A 2011 Hayes HTA reported the results from a search of the Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database (a searchable database that consists of voluntary reports of adverse events involving medical devices), revealing 13 reports of adverse events associated with hyperbaric oxygen chambers from 2009 to 2011 (Hayes, Inc., 2011). Most of the reported events were mild and included visual loss, ruptured ear drum, and malfunction (e.g., difficulty with decompression). There were 5 reports of seizures; 3 patients with no prior seizure history experienced

auditory seizures within a 2-week period of treatment, one of which turned into a grand mal seizure. Of the other two seizure reports, one involved a patient who subsequently died after developing a grand mal seizure while receiving HBOT (Hayes, Inc., 2011). A nonsystematic review by Roth and Weiss (1994) included in a 2008 Hayes HTA estimated oxygen seizures in 1 of 11,000 treatments. The report suggested that prolonged HBO exposures at 3 ATA would very likely result in seizures, whereas seizures are extremely rare at 2 ATA.

The Medical Services Advisory Committee (MSAC) of Australia examined the harms associated with HBOT as part of an update of a 2001 report assessing HBOT for the treatment of nonhealing wounds in nondiabetic patients and refractory soft tissue radiation injuries (MSAC, 2003). This good-quality report included 4 reviews (Tibbles and Edelsberg, 1996; Leach et al., 1998; Feldmeier, 2001; MSAC, 2001) and 4 observational studies (Plafki et al., 2000; Weaver and Churchill, 2001; HTNA and ANZHMG, 2002; Ohrui et al., 2002) reporting on harms. Overall, harms were rare and self-limiting, with most resolving after termination of treatment. The reported harms are outlined in Table 12; the most common included myopia, barotrauma, claustrophobia, and oxygen toxicity. Life-threatening adverse events were rare (MSAC, 2003).

Table 12. Harms Associated with HBOT – Data from MSAC (2003)

Adverse Event	Incidence	Source (# Patients or HBOT Sessions)
Overall incidence	6.3%	Ohrui et al. (2002) (58,454 HBOT sessions)
Death	0/21,033 (0%)	Hyperbaric Technicians and Nurses Association (HTNA) and Australian and New Zealand Hyperbaric Medicine Group (ANZHMG) (2002)*
Persistent ocular changes	1/112 (0.9%)	HTNA and ANZHMG (2002)
Ear barotrauma	1/170 (0.6%)	HTNA and ANZHMG (2002)
Sinus barotrauma	1/4864 (0.02%)	HTNA and ANZHMG (2002)
Pulmonary barotrauma	0/15,475 (0%)	HTNA and ANZHMG (2002)
Claustrophobia	1/910 (0.1%)	HTNA and ANZHMG (2002)
Central nervous system seizures	1/1548 (0.06%) 0.01%	HTNA and ANZHMG (2002) MSAC (2001)
Pulmonary oxygen toxicity	1/6766 (0.01%)	HTNA and ANZHMG (2002)
Pulmonary edema	3/1028 female pts w/ cardiac disease and reduced ventricular ejection fractions	Weaver and Churchill (2001) (13,658 patients)
Ear pain	4.8%	Ohrui et al. (2002) (58,454 HBOT sessions)
Sinus pain	0.86%	Ohrui et al. (2002) (58,454 HBOT sessions)
Abdominal pain	0.34%	Ohrui et al. (2002) (58,454 HBOT sessions)
Hypoxia	0.08%	Ohrui et al. (2002) (58,454 HBOT sessions)
Joint pain	0.05%	Ohrui et al. (2002) (58,454 HBOT sessions)
Toothache	0.03%	Ohrui et al. (2002) (58,454 HBOT sessions)
General pain or discomfort during compression	17%	Plafki et al. (2000) (11,376 HBOT sessions)
Tympanostomy tube placement	1.5% (12 events/782 patients)	Plafki et al. (2000) (11,376 HBOT sessions)

Two primary data studies reported harms among patients with a mix of indications (Al-Waili et al., 2006; Toklu et al., 2008). Al-Waili et al. (2006) conducted a small, poor-quality, pre-post test investigating the influences of HBOT on blood pressure (BP), heart rate, and blood glucose among 41 patients with a variety of indications, including osteomyelitis, ORN, necrotizing fasciitis, compromised skin grafts, and nonhealing wounds. They reported that 2 diabetic patients developed hypoglycemic symptoms during HBOT; 1 patient developed an asthma attack; 1 patient with hypertension developed anxiety, a severe

headache, and elevated BP; 1 patient developed ocular complications; and 2 patients developed ear pain (Al-Waili et al., 2006). Toklu et al. (2008) conducted a questionnaire among facilities using HBOT examining how patients with radiological evidence of pulmonary blebs or bullae were treated and to determine the prevalence of pulmonary barotrauma. A total of 266 questionnaires were mailed, with a 36.8% response rate. The authors found that a significant proportion (66.3%) of centers apply HBOT even in the presence of air cysts in the lungs. The incidence of lung barotrauma was very low at 0.0005% (9 reports among 2 million treatments from 7 centers).

Diabetic Nonhealing Wounds: Reported harms among patients with diabetic nonhealing wounds were rare and generally mild. Goldman (2009) found just 2 studies reporting harms; 1 ear barotrauma among 14 patients assigned to the HBOT group versus 0 in the control group (Kessler et al., 2003) and 1 cataract among 17 patients in the HBOT group versus 0 in the control group (Kalani et al., 2002). The systematic review by Wang et al. (2003) reported just 1 case of barotrauma among 115 patients with diabetic nonhealing wounds (Faglia et al., 1996). Similarly, Kranke et al. (2012) reported that among 8 included trials, 2 studies stated explicitly that there were no complications among patients receiving HBOT (Doctor et al., 1992; Abidia et al., 2003), 1 trial reported that 2 patients were removed from the hyperbaric chamber during treatment because of claustrophobia (Löndahl et al., 2010), and there were no harms reported in the other included studies (Kranke et al., 2012).

Nonhealing Wounds not Specific to Diabetes: Eskes et al. (2010) set out a priori to look at visual disturbances, barotrauma, oxygen toxicity, infection, and reoperations among patients with acute surgical and traumatic wounds. They reported 2 additional surgical procedures in 1 patient in the HBOT group versus 8 among 6 patients in the sham group (RR, 0.25; 95% CI, 0.06-1.02; NNT, 3). They also reported a lower rate of necrotic tissue in the HBOT versus sham group (1 patient versus 8 patients, respectively) (RR, 0.13; 95% CI, 0.02-0.9; NNT, 3). Similarly, Villanueva et al. (2004) set out a priori to look at visual disturbances, barotrauma, oxygen toxicity, and any other reported adverse event; in 2 included studies, they reported 3 barotrauma among 141 patients undergoing HBOT for the treatment of thermal burns. Garcia-Covarrubias et al. (2005) evaluated HBOT in the management of crush injuries and/or acute peripheral ischemia and reported just 1 unspecified serious complication of HBOT among 9 included studies.

Osteomyelitis: A systematic review by Lawson (2003) reported transient myopia, barotraumatic otitis, seizures secondary to O_2 toxicity; and pneumothorax and pulmonary edema as adverse events associated with HBOT in the treatment of osteomyelitis but could not estimate the frequency of these events (Lawson, 2003). One nonrandomized controlled trial included in the Lawson review reported 2 deaths, one associated with oxygen toxicity, the other associated with pulmonary edema (Esterhai et al., 1987). In addition, Hart (2012) reported that adverse events related to HBOT among patients with refractory osteomyelitis are rare, the most common of which are middle ear and sinus barotrauma, and suggested that these events are mild and self-limiting. Hart also cited transient myopia and the need for tympanostomy tubes among some patients as additional considerations when looking at adverse events (Hart, 2012). The review by Wang et al. (2003) reported 3 patients requiring tympanostomy tubes among 38 patients with osteomyelitis (Davis et al., 1986).

LRTI: A Cochrane Review by Bennett et al. (2012), looking at the effectiveness of HBOT for the treatment of LRTI, reported one fair-quality trial, which found no significant increase in the risk of death among HBOT patients compared with controls (RR of dying following HBOT, 0.84; 95% CI, 0.13-5.61) (Annane et al., 2004). No other study in the Bennett et al. (2012) review reported the comparative risk of adverse

events among groups but 4 RCTs (253 participants) reported overall adverse events (Bennet et al., 2012). In a trial of 150 participants, 16% complained of ear pain, 3% experienced transient myopia, and 1.7% suffered confinement anxiety (Clarke et al., 2008). Gothard et al. (2010), in a trial of 58 participants, reported 8% of patients with transient myopia, while Schoen et al. (2007) reported no adverse events, observing that HBOT was well tolerated. The review by Wang et al. (2003) reported one case of minor blurring in a study of patients with ORN (McKenzie et al., 1993).

TBI: A fair-quality RCT by Rockswold and colleagues (2010) (n=69) compared the effect of HBOT with normobaric hyperoxia on cerebral metabolism, intracranial pressure and oxygen toxicity in patients with severe TBI and found no evidence in cerebral or pulmonary oxygen toxicity with HBOT.

Bennett and colleagues, in a Cochrane Collaboration Systematic Review, pooled the results from 2 fair-quality trials (228 TBI patients) (Artru et al, 1976a; Rockswold et al., 1992) and found 15 (13%) TBI patients receiving HBOT had severe pulmonary complications compared with none in the control groups (RR, 15.57; 95% CI, 2.11-114.72). The NNT for one adverse effect was 8 (95% CI, 5-15) (Bennett et al., 2009). Another trial (168 TBI patients) included in the Bennett review (Rockswold et al., 1992) reported 2 TBI patients (2.3%) from the HBOT group with isolated generalized seizures compared with none in the control group; the difference was not significant (RR, 5.0; 95% CI, 0.24-102.6); the study also reported 2 patients (2.3%) with ear barotrauma in the HBOT group compared with none in control group, and once again, the difference was not significant (RR, 5.0; 95% CI, 0.24-102.6) (Bennett et al., 2009).

Cerebral Palsy: One-good-quality RCT (n=111) reported on the side effects associated with low pressure (1.75 ATA) HBOT administered to patients with cerebral palsy and found that HBOT was generally well tolerated (Muller-Bolla et al., 2006). The main adverse event was ear barotrauma, the RR for middle ear barotrauma among patients in the HBOT group versus controls was 1.5 (95% CI, 1.1-2.2). In addition, 5.4% of children in the HBOT group underwent myringotomy compared with none in the control group; 28.6% of children in the HBOT group had pharyngitis versus 14.8% of controls. Groups reported similar instances of ear pain, otitis, fever, dyspepsia, and vomiting. No neurological or pulmonary manifestations of oxygen toxicity were noted (Muller-Bolla et al., 2006). A 2003 AHRQ review by McDonagh et al. (2003) found 2 RCTs and 3 observational studies reporting adverse events among children receiving HBOT for the treatment of cerebral palsy. Collet et al. (2001) reported ear problems among 47% of children receiving HBOT versus 22% among controls (*P* significant but value NR). Packard (2000) reported a 12% seizure rate and found that 35% of patients reported ear problems. Chavdarov (2002) reported that 8% of 50 children stopped treatment due to adverse events, including seizures, and Machado (1989) reported 1 seizure in an observational study of 230 patients.

Headaches and Migraines: A Cochrane Collaboration Review by Bennett et al. (2008) looking at the effectiveness of HBOT for the treatment and prevention of migraines and cluster headaches found that 3 of 7 included studies reported adverse events. Myers and Myers (1995) and Di Sabato et al. (1993) noted no adverse events among 33 participants. Eftedal et al. (2004) reported 2 withdrawals due to claustrophobia, 1 upper respiratory chest infection, and 1 withdrawal following a pathological chest x-ray among 40 patients.

Multiple Sclerosis: A Cochrane Review by Bennett and Heard (2011) examining the effectiveness of HBOT for the treatment of multiple sclerosis found 4 RCTs (259 participants) that looked at the Incidence of visual disturbance during HBOT. In all, 71 (55%) patients suffered temporary deterioration in visual acuity in the HBOT group versus 3 (2.3%) in the sham group (OR, 24.87; 95% CI, 1.44-428.5;

NNT, 1; 95% CI, 1-2). In the same review, 6 trials (349 participants) considered the incidence of barotraumas. Among those, 45 (24.5%) patients suffered an episode of barotrauma in the HBOT group versus 15 (9.3%) in the sham group (OR, 2.94; 95% CI, 0.62-13.91). The difference was not significant (Bennett and Heard, 2011).

Sensorineural Hearing Loss: In a 2007 systematic review looking at the effectiveness of HBOT for the treatment of sensorineural hearing loss, no trials reported adverse events in a systematic way (Bennett et al., 2007). One fair-quality RCT reported 6 withdrawals (3 patients with middle ear barotrauma and 3 patients with confinement anxiety) (Pilgramm et al., 1985).

Occupational Safety: We did not find any study investigating outcomes related to the safety of HBOT facilities. However, a study included in a 2009 Hayes HTA reported hazards associated with hyperbaric facilities, including exposure to noise, fire risk, thermal stress, and risk of manual handling injuries (Ritchie et al., 2008). Medical personnel assisting patients in a multiplace chamber are susceptible to potentially lethal decompression sickness. Exposing the assisting medical personnel to 100% oxygen at the end of the treatment session reduces the risk of decompression illness (Hayes, Inc., 2009b).

Summary and Quality Assessment: Safety

Few studies report harms as a primary outcome and many of the most revealing data on harms come from poor-quality observational studies. We did not rate the quality of each individual study reporting harms but the evidence is consistent and generalizable. We suggest that there is moderate-quality evidence from across 15 systematic reviews, 4 additional primary data studies, and 4 reports that the harms associated with HBOT are usually mild and self-limiting, with most resolving after termination of treatment. The most common harms include myopia, barotrauma, claustrophobia, and oxygen toxicity. Life-threatening adverse events are rare but do occur on occasion and can include seizures and death. There is insufficient evidence to comment on specific risks for subpopulations.

Key Question #3: What is the differential effectiveness and safety of HBOT according to factors such as age, sex, race or ethnicity, disability, comorbidities, wound or injury duration and severity, and treatment setting?

Evidence of the differential effectiveness and safety of HBOT was obtained from the systematic reviews selected to answer KQ1, KQ1a, and KQ2. Of 21 included systematic reviews in this report, 6 provide evidence relevant to KQ3 (Wang et al., 2003; Bennett et al., 2007; Bennett et al., 2008; Bennett et al., 2009; Goldman, 2009; Nabil and Samman, 2011). In addition, 4 primary data studies (2 RCT, 1 pre-post study, and 1 cases series), not included in the selected reviews, report on differential effectiveness (Golden et al., 2006; Cekin et al., 2009; Muzzi et al., 2010; Kuar et al., 2012) and are included here. We also include relevant safety data reported in 2 recent Hayes HTAs (Hayes, Inc., 2008a; Hayes, Inc., 2009b). A number of systematic reviews planned subgroup analysis a priori but were unable to carry out the analysis because of a lack of data. For example, Kranke et al. (2012), in a systematic review to assess the benefits and harms of HBOT for the treatment of chronic wounds, had planned to look at wound severity at study enrollment but found that a subgroup analysis was not possible because of the paucity of studies and poor reporting.

Findings, Differential Effectiveness

We found no relevant data on the differential effectiveness and safety of HBOT according to sex, race, ethnicity, disability, wound severity, duration, or treatment setting. Most of the studies reported whether patients were treated in monoplace or multiplace chambers but none directly compared the two and an indirect meta-analysis would be inappropriate due to significant heterogeneity between the studies. Wang and colleagues, in a large 2003 HTA to determine the effectiveness of HBOT for hypoxic wounds, reported that no studies addressed the issues of efficacy or safety differences between monoplace and multiplace chambers (Wang et al., 2003). Also, in relation to differential effectiveness, Bennett et al. (2008) looked at the effectiveness of HBOT for the treatment and prevention of migraines and cluster headaches and suggested that HBOT should possibly be reserved for those patients resistant to standard pharmacological treatments, noting, however, that there are currently no studies to provide evidence of effectiveness for this subgroup of patients (Bennett et al., 2008). The following section outlines the available evidence for the differential effectiveness and safety of HBOT according to age, wound severity, severity of sensorineural hearing loss, levels of radiation exposure among patients with LRTI, response to transcutaneous oxygen measurement (TCOM) among a group of children with brain injury, and comorbidities.

Age: A fair-quality RCT (57 participants) found no significant difference in hearing recovery among patients < 50 years of age compared with those ≥ 50 years of age (P>0.05) (Cekin et al., 2009). In contrast, a poor-quality case series of 19 patients found that HBOT provided to patients who had failed other common treatments for sensorineural hearing loss improved hearing significantly more among patients ≥ 50 years of age compared with those < 50 years of age (absolute improvement among patients ≥ 50 years of age 14.38 dB, absolute improvement among patients < 50 years of age 4.47 dB; P=0.037 at low frequencies but not significant at higher frequencies) (Muzzi et al., 2010).

Severity of Sensorineural Hearing Loss: Evidence of a difference in the effectiveness of HBOT according to severity of hearing loss is mixed. A 2007 systematic review (Bennett et al., 2007) investigating the effectiveness of HBOT for the treatment of sensorineural hearing loss pooled data from 2 RCTs (1 fair quality, 1 poor quality) (Pilgramm et al., 1985; Topuz et al., 2004) and found a significant improvement in mean hearing across all frequencies with HBOT among those with severe hearing loss (n=14) at enrollment (MD, 37.7 dB; 95% CI, 22.9-52.5) but not among those with mild hearing loss (n=19) at enrollment (MD, 0.2; 95% CI, –10 to 10.4). In contrast, the review authors reported one poor-quality trial, which looked at severity of hearing loss as a subgroup (Cavallazzi et al., 1996). Cavallazzi and colleagues found no significant difference in either a 25% or 50% improvement in hearing loss with HBOT by severity of loss. The RR for hearing improvement of 50% with HBOT in mild hearing loss was 1.54 (95% CI, 0.79-2.55) versus an RR of 1.07 (95% CI, 0.29-3.88) for severe hearing loss. The RR for hearing improvement of 25% with HBOT in mild hearing loss was 1.32 (95% CI, 0.86-2.02) versus an RR of 1.28 (95% CI, 0.56-2.91) for severe hearing loss (Cavallazzi et al., 1996).

Radiation Exposure: Based on weak data from 9 included studies(1 RCT, 8 observational), a fair-quality systematic review by Nabil and Samman (2011) reported no cases (following post-irradiation extraction) of ORN among 29 patients receiving a radiation dose < 60 grays (Gy), but 28 cases (12%) among patients having received a radiation dose > 60 Gy following post-irradiation extraction. They concluded that, in the absence of contraindications, patients having received a radiation dose > 60 Gy for the treatment of head and neck cancer and requiring extraction of mandibular teeth within the radiated field are at the highest risk of developing ORN and may benefit most from HBOT (Nabil and Samman, 2011).

Response to TCOM: A number of studies looked at whether response of nonhealing wounds to normobaric elevated oxygen levels (i.e., elevated oxygen breathed under normobaric conditions outside of a hyperbaric chamber) can determine which patients are most likely to benefit from HBOT. A systematic review by Goldman (2009) reported a poor-quality retrospective cohort of 36 patients having received HBOT for the treatment of arterial ulcers (Grolman et al., 2001). The authors investigated TCOM could be used to identify patients most likely to benefit from HBOT. TCOM was measured with the patient breathing room air while breathing 100% oxygen at ambient pressure. Healing was observed in 70% of patients with ΔTCOM > 10 millimeters of mercury (mm Hg) versus 11% healing in patients with ΔTCOM < 10 mm Hg) (P<0.01), suggesting that patients with an increase of tissue oxygen tension ≥ 10 torr when breathing pure oxygen may benefit from HBOT, whereas patients with an increase of < 10 torr are unlikely to receive benefit (Grolman et al., 2001). Similarly, the Wang et al. (2003) review reported on a poor-quality case series of 23 patients with acute traumatic peripheral ischemia and found that TCOM predicted the risk of amputation among patients breathing normal air, normobaric oxygen, or hyperbaric oxygen (Mathieu et al., 1990). A large HTA by Wang et al. (2003) reported a number of case series that measured whether patients' tissue oxygen level during HBOT was predictive of response. They described a case series by Wattel and colleagues (1990) where wounds of 20 patients with chronic arterial insufficiency ulcers or diabetic ulcers healed if they were able to achieve a distal transcutaneous tissue oxygen level of at least 100 mm Hg during HBOT therapy. Complete healing occurred in 15 of 20 patients. Wang et al. (2003) also reported a case series of 15 patients undergoing musculocutaneous flap transplantation, finding that transcutaneous oxygen (PtcO2) measurements in HBOT predict patients who will undergo amputation (Mathieu et al., 1993). Furthermore, a very recent small RCT (n=30) (found during the update search) reported a positive correlation between transcutaneous oxygen measurement and a decrease in wound area (P=0.004) (Kuar et al., 2012).

Comorbidities: A nonsystematic review included in a 2008 Hayes HTA reported that untreated pneumothorax is the only absolute contraindication to HBOT (Roth and Weiss, 1994); lung disease, previous ear surgery or trauma, significant upper respiratory infections, fever, and claustrophobia are considered relative contraindications, depending on their severity. In addition, some consider preexisting cataracts, optic neuritis, and pregnancy to be relative contraindications (Roth and Weiss, 1994). Roth and Weiss also suggest that certain medications, including steroids, amphetamines, catecholamines, insulin, and thyroid hormone, may enhance central nervous system oxygen toxicity, and suggested that patients who are receiving these and other medications should be monitored closely during HBOT (Roth and Weiss, 1994). Al-Waili et al. (2006) conducted a small, poor-quality pre-post test investigating the influences of HBOT on blood pressure (BP), heart rate, and blood glucose among 41 patients with a variety of indications (including osteomyelitis, ORN, necrotizing fasciitis, compromised skin grafts, and nonhealing wounds) and found that underlying diseases and concomitant medical treatments significantly influence the effects of HBOT on vital signs. Overall, mean systolic and diastolic BP were significantly higher post HBOT (MD, 7 mm Hg; P=0.001 and MD, 8.9 mm Hg; P<0.001, respectively). Heart rate decreased by 18% (P<0.001), and blood sugar levels dropped from 231 mg/dL (SD, 95) pretreatment to 170 mg/dL (SD, 85.8) posttreatment (P<0.001). The authors found that patients with diabetes and hypertension suffered higher elevations in systolic BP and a greater drop in heart rate than did comparison groups (Al-Waili et al., 2006). (NOTE: There were inconsistencies between the text and tables in the study and we have low confidence in the reliability of the results.)

Findings, Differential Safety

No study directly compared harms between subpopulations. However, a number of studies looked at HBOT-related harms within certain subpopulations, which helps shed light on differences that may exist between groups. Weaver (2011) conducted a systematic review to assess HBOT treatment for critically ill, intubated, mechanically ventilated patients and reported no HBOT-related deaths among 3 included observational studies (450 patients) (Lo et al., 2005; Weaver et al., 2006; Rockswold et al., 2010). Among the included studies, Rockswold et al. (2010) reported no evidence of oxygen toxicity, and Weaver et al. (2006) reported 2.7% (35 of 1281 sessions) of treatment session needed to be terminated early due to complications necessitating decompression from the chamber.

Summary and Quality Assessment: Differential effectiveness and safety

Table 13 summarizes the results for the differential effectiveness of HBOT. There is very-low-quality evidence suggesting that younger TBI patients may recover faster with HBOT than older patients. There is low-quality evidence suggesting that radiation dose influences the effectiveness of HBOT to prevent ORN among head and neck cancer survivors. There is also low-quality evidence that TCOM may predict those most likely to benefit from HBOT. There is insufficient evidence from poor-quality studies to determine the differential safety of HBOT across populations. Additionally, there is insufficient evidence from poor-quality studies to determine the differential safety of HBOT across populations and indications. There is no evidence to determine the differential effectiveness and safety of HBOT according to sex, race, ethnicity, disability, wound duration, or treatment setting.

Table 13. Differential Effectiveness of HBOT

Factor/Indication	Findings	Source of Evidence	Quality of Evidence
Age/sensorineural hearing loss	Mixed results but a fair-quality RCT suggests that age is not related to the effectiveness of HBOT	1 fair-quality RCT, 1 poor-quality case series	Low
Radiation exposure/late radiation tissue injury (LRTI)	Higher incidence of osteoradionecrosis (ORN) following extraction of mandibular teeth among head and neck cancer patients who received radiation doses >60 grays (Gy) (compared with doses <60 Gy), suggesting that HBOT may be more effective among patients exposed to >60 Gy of radiation therapy	1 fair-quality RCT, 1 fair-quality observational study, 6 poor-quality observational studies	Low
Age/traumatic brain injury (TBI)	Improved effectiveness among younger patients	1 fair-quality trial	Very low
Severity of sensorineural hearing loss	Insufficient evidence, based on mixed results, regarding the effectiveness of HBOT according to the severity of hearing loss	1 fair-quality RCTs, 2 poor-quality RCTs	Low
Transcutaneous oxygen measurement (TCOM)	TCOM predicts effectiveness of HBOT	1 fair-quality RCT; 4 poor-quality observational studies	Low
Comorbidities	• Comorbidities such as lung	1 poor-quality pre-post test and	Low

Factor/Indication	Findings	Source of Evidence	Quality of Evidence
	disease, previous ear surgery or trauma, significant upper respiratory infections, fever, claustrophobia, preexisting cataracts, optic neuritis, and pregnancy are contraindications for HBOT • Hypertensive and diabetic patients are at increased risk for HBOT-related harms	1 nonsystematic review without quality assessment	

Key Question #4. What are the cost implications of HBOT, including the cost-effectiveness, compared to alternative treatments?

Cost

Cost estimates on the provision of HBOT are sparse. A 2006 UK-based cost-analysis estimated capital start-up costs between GBP 64,800 to 72,000 (USD 104,985-116,650) (conversion to USD using rate on September 20, 2012), and cost per treatment ranging from GBP 32 to 41 (USD 52-66) (Treweek and James, 2006). Data were based on 10 years of gathered data and refer to providing HBOT in a monoplace chamber to inpatients in a teaching hospital. Older data from the U.S. reported costs in 1996 of USD 300 to 400 for an average 90-minute session. The average total allowed charge per treatment in the U.S. in 1998 was USD 405, with an average allowed therapy cost per patient of approximately USD 12,000.

Economic Evaluations

Two good-quality systematic reviews were selected to answer KQ4 (De Laet et al., 2008; Ritchie et al., 2008). Together they include 11 studies. The Belgian Health Care Knowledge center (KCE) undertook a systematic review to determine the cost-effectiveness of HBOT compared with standard care across indications (De Laet et al., 2008). They identified 6 cost-effectiveness analyses (Wheen, 1994; Dempsey et al., 1997; MSAC, 2001; Guo et al., 2003; MSAC, 2003; Hailey et al., 2007) and 1 RCT with cost estimate comparisons (Abidia et al., 2003). The UK National Health Service (NHS) also conducted a systematic review to determine the cost-effectiveness of HBOT compared with standard therapies (Ritchie et al., 2008). Five of 7 studies included in the KCE report were also included in the NHS report (Dempsey et al., 1997; MSAC, 2001; Abidia et al., 2003; Guo et al., 2003; Hailey et al., 2007). In addition, the NHS report included 3 UK-based cost analyses (Cianci et al., 1990; Ward et al., 2000; Treweek and James, 2006). The following details the results (by indication) from each of the 11 included studies.

Diabetic Wounds: Five studies reported economic evaluations related to the use of HBOT for diabetic wounds:

- Wheen (1994) conducted a cost-utility analysis from the payer perspective on the costs associated with HBOT to manage diabetic foot ulcers. The average cost for treating a non-HBOT

patient was NZ 38,359 (USD 31,680), versus NZ 31,026 (USD 26,624) for HBOT patients at public hospital bed costs, and NZ 10,565 (USD 8726) for HBOT patients at navy hospital bed cost estimates (conversion to USD using rate on September 20, 2012).

- The Medical Services Advisory Committee (MSAC) of Australia carried out a cost-effectiveness analysis in 2000 investigating the cost-effectiveness of HBOT versus alternative procedures for patients with diabetic wounds. Neither the perspective, time horizon, nor the discount rates used were provided. The authors reported the cost of avoiding one major lower extremity amputation with the addition of HBOT was AUD 11,142 (USD 11,611), and the cost of avoiding any amputation with HBOT was AUD 22,054 (USD 22,983). The results were sensitive to the assumptions of the model, particularly the number of HBOT sessions and the efficacy assumptions used, suggesting that the model was not robust (MSAC, 2001).
- A U.S.-based study by Guo et al. (2003) used a decision tree analysis to calculate the cost-effectiveness of standard care plus adjunctive HBOT versus standard care alone among patients with severe diabetic foot ulcers. The time period was 1, 5, and 12 years, with the 12-year estimate representing the societal perspective and the other years representing the payer perspective. A discount rate of 3% was employed, and the results were given in 2001 USD. The authors' estimated quality-adjusted life-years (QALYs) gained at years 1, 5, and 12 resulting from use of HBOT were 50.2, 265.3, and 608.7, respectively. The corresponding ICERS were USD 27,310 at year 1, USD 5166 at year 2, and USD 2255 by year 12. Guo and colleagues concluded that HBOT was cost-effective, especially in the long term but recognized that the ICERs were very sensitive to the assumption of the model, making the model estimates unreliable (Guo et al., 2003).
- An RCT by Abidia et al. (2003) reported a potential mean savings (from the payer perspective) of GBP 2960 (USD 4796) per patient, in favor of adjunctive HBOT (2003 UK pounds), when the mean total costs of visits for diabetic ulcer dressings per patient per year among patients receiving standard care were compared with the mean total costs of HBOT and its associated complications among patients receiving standard care and adjunctive HBOT (Abidia et al., 2003) (conversion to USD using rate on September 20, 2012).
- Hailey et al. (2007) conducted a decision tree analysis calculating costs per QALY gained for patients with diabetic foot ulcers treated with standard wound care versus standard wound care plus adjunctive HBOT. The perspective was both societal and for that of the ministry for health, the time horizon was 12 years, the discount rate was not reported, and the year for costs was 2004 CAD. The results suggested that adjunctive HBOT was dominant over standard care alone with 3.64 QALY gained among the HBOT group versus 3.01 among controls. The 12-year cost to the patient was CAD 40,695 (USD 41,625) for the HBOT group and CAD 49,786 (USD 50,924) for controls. The results remained stable in a sensitivity analysis, suggesting that the model was robust and reliable (Hailey et al., 2007).

Nondiabetic Nonhealing Wounds: The 2003 MSAC report suggested that among patients with nondiabetic nonhealing wounds, the treatment costs for a one third reduction in wound size with HBOT were AUD 6941 (USD 7233) per patient per 30 HBOT sessions (conversion to USD using rate on September 20, 2012). The cost-effectiveness (we assume a payer perspective) to cure 1 person of a chronic leg ulcer was AUD 27,764 (USD 28,933). However, the model was sensitive to the assumptions and, therefore, we have low confidence in the estimates provided.

ORN: Three studies looking at the cost-effectiveness of HBOT for the treatment of ORN found HBOT to be cost effective, but all were sensitive to the assumptions of the models, making the results unreliable.

- Dempsey et al. (1997) conducted a cost-effectiveness analysis on HBOT for ORN of the mandible. The perspective was societal, the discount rate was 5%, costs were provided in 1995 Canadian dollars, and the time horizon was not reported. They found HBOT to be dominant over the hypothetical control, estimating cost savings of CAD 53,147 (USD 54,362) with HBOT versus controls (conversion to USD using rate on September 20, 2012). The results were sensitive to the assumptions of the model, particularly the number of days in hospital, indicating that the model was not robust (Dempsey et al., 1997).
- The 2001 MSAC report (payer perspective) estimated an incremental cost-effectiveness ratio (ICER) of AUD 28,480 (USD 29,680) to avoid 1 case of ORN with the addition of HBOT. Once again, this estimate was sensitive to the assumptions of the model, indicating that the model was not robust.
- Ward et al. (2000) conducted a crude cost-effectiveness analysis on the use of HBOT to treat ORN following dental extraction in an irradiated field and found the estimated cost per patient per year for HBOT was GBP 20,000 (USD 32,403) versus GBP 5000 (USD 8101) among non-HBOT controls (assumed payer perspective). Sensitivity analysis suggested that the break-even costs of treating ORN with HBOT ranged from GBP 17,500 to 127,500 (USD 28,352-206,568) (conversion to USD using rate on September 20, 2012).

Burns: A poor-quality U.S. study by Cianci et al. (1990) included a payer perspective cost-effectiveness analysis as part of a nonrandomized trial comparing HBOT plus standard wound care with standard wound care alone among 21 patients with 19% to 50% total body surface area burns. The perspective was that of the healthcare provider, the time horizon was the period of the study, and the results were in 1987 U.S. dollars. The authors found that the HBOT group had an average decrease in the length of hospital stay of 14.8 days compared with controls, a reduction in surgical procedures of 39%, and an average saving per case of USD 31,600 (Cianci et al., 1990). This result conflicts with the efficacy data reported earlier, suggesting that there is insufficient evidence to support the use of HBOT for the treatment of burns.

Summary and Quality Assessment: Cost implications

HBOT may be cost effective under very specific assumptions of effectiveness and costs. All included cost analyses found HBOT to be cost effective or cost saving. However, the available economic evaluations were severely limited by sparse cost data and/or unreliable efficacy estimates used to make model assumptions. For example, our report found insufficient evidence in the case of burns, for the effectiveness of HBOT for treating nonhealing nondiabetic wounds, so any data on cost-effectiveness are seriously limited by the adequacy of the effectiveness data used for the base-case parameters. While we found moderate-quality effectiveness data for the use of HBOT for diabetic nonhealing wounds and for treating ORN (suggesting more confidence in the estimates used for these indications), all cost-effectiveness results were found to be very sensitive to model assumptions. Only one model was found to be robust during sensitivity analysis, making most estimates very unreliable. Overall, there is a low quality of evidence to suggest that HBOT may be a cost-effective treatment under certain conditions, for certain populations and indications, but current data are insufficient to determine the most cost-effective uses of the technology.

PRACTICE GUIDELINES

Of 27 guidelines reviewed, 14 were selected as relevant to this report. Key guideline recommendations are described below under the relevant indication or subgroup. In addition, Table 14 summarizes the evidence sources used by each guideline group in developing recommendations and provides a quality assessment for each guideline, determined using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument (AGREE Enterprise, 2009).

Cross-Cutting Guidelines

The following 2 guidelines are cross-cutting providing recommendations relevant to the use of hyperbaric oxygen therapy (HBOT) for multiple indications.

The **European Committee for Hyperbaric Medicine (ECHM)** and the **European Tissue Repair Society** (ETRS) (Niinikoski et al., 2007) produced recommendations as part of an ECHM-ETRS joint conference on oxygen and tissue repair (*good quality*) held in Italy in October of 2006 (Niinikoski et al., 2007). Relevant recommendations from that report include the following:

- HBOT is not required in situations where normal wound healing is anticipated. Its primary role is restricted to certain situations of impaired or delayed wound healing.
- HBOT can be used when standard care fails to achieve oxygen levels necessary for normal wound healing: type II recommendation (i.e., evidence is convincing).
- The two main conditions that can be considered for adjunctive HBOT are infection (i.e., periwound cellulitis, bone and joint infection) and ischemia.
- Presently, there is reliable evidence that HBOT is effective in reducing major amputations in patients with diabetic foot ulcers (level 2 – convincing evidence); but there is a paucity of reliable evidence of the value of HBOT in patients with lower extremity wounds of other etiologies.
- A significant saving can be achieved using HBOT as a standard adjunct in treating necrotizing infections, diabetic ulcers, and radiation necrosis as currently recommended by the ECHM and Underwater and Hyperbaric Medical Society (UHMS). The number of HBOT treatments has a significant impact on cost-effectiveness ratios. Clinical guidelines are recommended to assure optimal cost-effectiveness: type I recommendation (i.e., strongly recommended, supported by strong evidence).
- Before HBOT is considered, patients should undergo a complete clinical evaluation with correction of systemic and local factors responsible for delayed healing. These include cessation of smoking, pressure measures, glycemic control etc.: type I recommendation (i.e., strongly recommended, supported by strong evidence).
- The possibilities of revascularization must be considered and either performed or the possibility excluded: type I recommendation (*strongly recommended, supported by strong evidence*).
- When HBOT is planned to correct wound ischemia (hypoxia), wound hypoxia and its correction under hyperbaric conditions should be measured using objective methods: type I recommendation (i.e., strongly recommended, supported by strong evidence).
- Oxygen concentration should be measured in both the wound and in normal tissues: type I recommendation (i.e., strongly recommended, supported by strong evidence).

- Clinical staff interested in HBOT for wound healing should be properly trained and encouraged to use tools already developed in order to quantify clinical results: type I recommendation (i.e., strongly recommended, supported by strong evidence).
- Hyperbaric teams should be multidisciplinary, including specialists in a variety of fields and in basic science: type I recommendation (i.e., strongly recommended, supported by strong evidence).
- Medical staff involved in wound care and hyperbaric medicine should receive regular training in basic and clinical research methods (e.g., in the form of continuing medical education [CME]): type I recommendation (i.e., strongly recommended, supported by strong evidence).

The **Wound Healing Society (2006)** formed an advisory panel of academics, private practice physicians, nurse clinicians, and research nurses from across the U.S. to develop guidelines (minimum standards) for the treatment of arterial insufficiency ulcers of the lower extremities (both diabetic and nondiabetic related) **(**Hopf et al., 2006) (fair quality). The following recommendations are relevant to the current report:

- In patients with nonreconstructable anatomy or whose ulcer is not healing despite revascularization, HBOT should be considered as an adjunct therapy.
  - Diabetic ischemic ulcers received a Level 1A recommendation meaning that it is strongly recommended and likely to be of benefit with evidence supported by meta analysis of multiple RCTs and/or ≥ 2 RCTs or multiple laboratory or animal studies supported by 2 or more clinical case series.
  - Nondiabetic ischemic ulcers received a Level IIB recommendation meaning that the evidence is supported by ≥ 1 RCT and 2 or more clinical case series or expert opinion with literature reviews.
- HBOT should be investigated in the treatment of ischemia-reperfusion injury after revascularization in patients with arterial ulcers

Diabetic Wounds, Including Diabetic Foot Ulcers

Two guidelines provided recommendations specific to diabetic foot ulcers: **National Institute for Health and Clinical Excellence (NICE) (2011)** in the UK developed a guideline on the inpatient management of diabetic foot problems (NICE, 2011) (good quality). Information and recommendations specific to the use of HBOT include the following:

- Do not offer HBOT as an adjunctive treatment for the inpatient management of diabetic foot problems, unless as part of a clinical trial.
- Further research should be undertaken to determine the clinical and cost-effectiveness of HBOT for diabetic foot problems.

The **Wound Healing Society (2006)** formed an advisory panel of physicians from academia and private practice, nurses, a podiatrist, a pedorthist, and a representative from industry from across the U.S. to develop guidelines for the treatment of diabetic ulcers of the lower extremity (Steed et al., 2006) (fair quality) and recommended that HBOT may be of benefit in reducing the amputation rate in patients with ischemic diabetic foot ulcers. This recommendation was given a level 1 evidence grade, meaning that the evidence was supported by meta-analysis of multiple RCTs and /or ≥ 2 RCTs or multiple laboratory or animal studies supported by 2 or more clinical case series.

Other Nonhealing Wounds

We found 6 guidelines pertaining to nonhealing wounds other than diabetic wounds. Four relate to pressure ulcers, one to lower extremity amputations (not related to diabetes), and one to nonhealing ischemic wounds.

The **Institute for Clinical Systems Improvement (ICSI) (2012)** published a protocol for the treatment of pressure ulcers (ICSI, 2012) (fair quality) and provided the following HBOT-related recommendation based on consensus reports: HBOT is generally not the first adjunct therapy considered for the treatment of pressure ulcers since wound ischemia is due to pressure that should be eliminated through support surfaces, splinting, and positioning. If offloading measures are adequate, the wound should get enough perfusion, as long as no arterial insufficiency is present.

The **European Pressure Ulcer Advisory Panel** and **National Pressure Ulcer Advisory Panel (2009)** produced pressure ulcer prevention and treatment recommendations in the Clinical Practice Guidelines (good quality) and suggested that there is insufficient evidence to recommend HBOT for the treatment of pressure ulcers.

The **Registered Nurses' Association of Ontario (2007)** published a report on the assessment and management of stage I to IV pressure ulcers (good quality) and recommended that chronic pressure ulcers may be treated by HBOT. This recommendation was given level IV evidence grade (i.e., the evidence was obtained from expert committee reports or opinions and/or clinical experiences of respected authorities).

The **Association for the Advancement of Wound Care (2010)** published a report titled the Association for the Advancement of Wound Care guideline of pressure ulcer guidelines (good quality) and suggested that HBOT is not recommended as an adjunctive treatment if pressure ulcers are unresponsive to A-level management. They gave this recommendation a level C rating, meaning that the results were based on one controlled trial, or at least two case series or descriptive studies or a cohort study in humans or on expert opinion. The report added that HBOT may be useful if an ischemic condition or osteomyelitis is present (level C evidence rating).

The **Department of Veterans Affairs and Department of Defense (VA/DOD) (2007)** produced a joint clinical practice guideline for rehabilitation of lower extremity amputation (fair quality) and recommended HBOT as an adjunct treatment for impaired postoperative wound healing.(no recommended grade was provided).

The **Wound, Ostomy and Continence Nurses Society (2008)** produced a guideline for the management of wounds in patients with lower-extremity arterial disease (Bonham et al., 2008) (fair quality) and recommended that HBOT be considered for patients with nonhealing, ischemic ulcers. A level B evidence grade was assigned (i.e., evidence was based on 1 or more supporting controlled trials of at least 10 humans with lower-extremity arterial disease or 2 or more supporting nonrandomized trials of at least 10 humans with lower-extremity arterial disease).

Cerebral Palsy

The Canadian **Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) (2007)** produced guidelines on the place of HBOT in the management of cerebral palsy (fair quality). The following recommendations from the report relate to the use of HBOT for the treatment of cerebral palsy:

- The efficacy of HBOT in the management of cerebral palsy should be the subject of a newly funded research project.
- HBOT should not be generally prescribed by physicians, except in the case of a formal research project.
- Physicians treating children with cerebral palsy should inform parents wishing to use HBOT of the unrecognized status of this treatment modality, and how to minimize its associated risks.

Sudden Sensorineural Hearing Loss

The **American Academy of Otolaryngology – Head and Neck Surgery (Stachler et al., 2012)** published a clinical practice guideline on sudden hearing loss (good quality) and recommended the following relevant to HBOT:

- Clinicians may offer HBOT within 3 months of diagnosis of sudden sensorineural hearing loss (SSHL). This recommendation is based on aggregate evidence with a quality grade B based on systematic review of RCTs with methodological limitations.
- Although HBOT is not widely available in the United States and is not recognized by many U.S. clinicians as an intervention for SSHL, the panel acknowledged that the level of evidence for hearing improvement, albeit modest and imprecise, was sufficient to promote greater awareness of HBOT as an intervention for SSHL.
- The recommendation pertains to patients with acute SSHL presenting within 3 months of onset.

ORN

The **Dutch Head and Neck Oncology Cooperative Group (2007)** published a guideline on hypopharyngeal cancer (fair quality) recommending that HBOT be considered for the treatment of mandibular ORN. No other details were provided.

Critically Ill Patients

Weaver (2011) published a systematic review with the following guidelines specific to HBOT for critically ill intubated, mechanically ventilated patients (poor quality):

Facilities, equipment, and staffing:

- All equipment used inside hyperbaric chambers must adhere to the guidelines of the National Fire Protection Association (NFPA) and be tested for the pressures to which they will be exposed.
- Hyperbaric oxygen can be offered to critically ill patients in both monoplace and multiplace chambers.

- The potential benefits of HBOT to a critically ill patient must be balanced by the risks from transporting the patient as well as the risks from HBOT.
- Personnel working as inside attendants of multiplace chambers must be medically suitable for hyperbaric exposure (e.g., able to equalize ears, no claustrophobia, no pulmonary or cardiac disease, etc.) In addition, they must follow safe "diving" practices and adhere to decompression tables.
- Hyperbaric medicine services that treat critically ill patients must be equipped to monitor the patient to the standards of an ICU, including electrocardiogram, blood pressure, and pulse oximetry.

Treatment protocol for the critically ill:

- Pressure, duration, and number of treatment sessions should vary, depending on the indication; compromised flaps should be treated with 2 atmospheres absolute (ATA) twice daily for several days.
- Partial pressure of oxygen in the blood (PaO_2) may influence the efficacy of HBOT; immediately post HBOT, intubated pts may require a higher fractional inspired oxygen concentration than before HBOT, which resolves within hours; critically ill patients requiring fractional inspired oxygen concentration > 0.4 to maintain adequate PaO_2 may need to breathe air intermittently to reduce the risk of oxygen toxicity.
- There is no consensus on whether critically ill pts might benefit from prophylactic myringotomies or tympanostomy tubes before HBOT.
- Critically ill children can be treated with HBOT in monoplace or multiplace chambers. However, complications from HBOT in critically ill children are rarely reported; therefore, input and co-management by pediatric intensive care is invaluable.
- Before compressing patients with implanted pacemakers and intracardiac defibrillators, the manufacturer must specify that the device is suitable for hyperbaric compression, including to its maximum pressure limit.
- In the monoplace environment, the chamber must be decompressed and the patient removed before performing defibrillation or cardioversion.

Table 14. Evidence Source and Quality Assessment for Included Guidelines

Author and Date Organization	Indication/ Subgroup	Evidence Source Employed by the Guideline	AGREE Quality Assessment (Scale 0-7)
European Committee for Hyperbaric Medicine (ECHM) and European Tissue Repair Society (ETRS) (Niinikoski et al., 2007)	Cross-cutting	Not reported	6
Wound Healing Society (Hopf et al., 2006)	Cross-cutting	Previous guidelines; MEDLINE; Embase; Cochrane Library; reviews of arterial ulcer treatment; Medicare/Centers for Medicare & Medicaid Services (CMS)	5
NICE (2011)	Diabetic foot	Allied and Complementary Medicine Database; British Nursing Index; Health Business Elite; Cochrane Database of Systematic Reviews (CDSR); Cochrane Central Register of Controlled Trials (CENTRAL); Database of Abstracts of Reviews of Effects (DARE); health technology assessments (HTAs); CINAHL; Embase (Ovid); Health Management Information Consortium (HMIC); MEDLINE; PsycINFO	6
Wound Healing Society (2006)	Diabetic foot ulcers	Previous guidelines; MEDLINE; Embase; Cochrane Library; recent reviews of diabetic foot ulcers; Medicare/CMS consensus of usual treatment of chronic wounds	5
Institute for Clinical Systems Improvement (ICSI) (2012)	Pressure ulcers	Electronic databases (specifics NR)	5
European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel (2009)	Pressure ulcers	PubMed; CINAHL; Embase; CDSR; Cochrane Central; Register of Controlled Trials; HTAs; Allied and Alternative Medicine Database (AMED) (inclusive dates January 1998 – January 2008); 13 sets of pressure ulcer guidelines (approximately 3000 published manuscripts reviewed)	7
Registered Nurses' Association of Ontario (2007)	Pressure ulcers	MEDLINE; Embase; CINAHL	6
Association for the Advancement of Wound Care (2010)	Pressure ulcers	Manual searches of published literature (primary sources); manual searches of published Literature (secondary sources); searches of electronic databases; searches of unpublished data	6
Department of Veterans Affairs (VA)/Department of Defense (DOD) (2007)	Management of lower extremity amputations	MEDLINE/PubMed; DARE; CENTRAL	5
Wound, Ostomy and Continence Nurses Society (Bonham et al., 2008)	Nonhealing ischemic wounds	MEDLINE; CINAHL; Cochrane Library	5

Author and Date Organization	Indication/ Subgroup	Evidence Source Employed by the Guideline	AGREE Quality Assessment (Scale 0-7)
American Academy of Otolaryngology – Head and neck Surgery (Stachler et al., 2012)	Sudden sensorineural hearing loss	National Guideline Clearinghouse; Cochrane Library; CINAHL; Embase; PubMed; Web of Science; BIOSIS; CENTRAL; CAB Abstracts; CMA Infobase; NHS Evidence; ENT and Audiology; National Library of Guidelines; NICE; Scottish Intercollegiate Guidelines Network (SIGN), New Zealand Guidelines Group (NZGG); Australian National Health and Medical Research Council; Tripdatabase; DARE HTA Database; Health Services Technology Assessment Texts (HSTAT)	7
Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) (2007)	Cerebral palsy	CINAHL; dissertation abstracts; Cochrane Library; psychological abstracts; PubMed; Embase; World of Science; textbooks; websites of the Undersea and Hyperbaric Medical Society (UHMS), National Institute of Neurological Disorders and Stroke (NINDS), United Cerebral Palsy Association	5
Dutch Head and Neck Oncology Cooperative Group (2007)	Osteoradionecrosis (ORN)	Cochrane Library; MEDLINE; Embase; CINAHL; PsycINFO	5
Weaver (2011)	Critically ill intubated, mechanically ventilated patients	MEDLINE; research repository of the Rubicon Foundation to find publications not indexed in PubMed; abstracts and reports presented at scientific meetings; clinical trial registries	2

Summary: Practice guidelines

We did not find guidelines on the use of HBOT for the treatment of multiple sclerosis, headaches and migraines, or brain injury. Refractory osteomyelitis was not the focus of any review but was mentioned in at least one included guideline. In all, we included 14 generally good-quality guidelines. Two were cross-cutting in nature covering multiple indications, 2 were specific to the use of HBOT for the management of diabetic foot ulcers, 4 provided guidelines on the use of HBOT for pressure ulcers, 1 on the management of lower-extremity amputations, 1 on nonhealing ischemic wounds, 1 on ORN, 1 on cerebral palsy, 1 on sensorineural hearing loss, and 1 systematic review, which provided guidelines for the use of HBOT among critically ill intubated, mechanically ventilated patients.

Cross-cutting: Two guidelines (1 good quality, 1 fair quality) were consistent with the evidence recommending HBOT only in cases of nonhealing wounds where standard care has not been effective and recognizing that the level of evidence pertaining to diabetic wounds is stronger than the evidence for other nonhealing wounds.

Diabetic nonhealing wounds: The Wound Healing Society in the U.S. recommended considering HBOT for diabetic foot ulcers based on moderate evidence (fair-quality guideline). In contrast, despite the guidelines recognition of moderate-level evidence for the use of HBOT for diabetic foot ulcers, NICE, in the UK, recommended against the use of HBOT for inpatients with diabetic foot ulcers unless as part of a clinical trial in a good-quality guideline.

Other nonhealing wounds: Consistent with the evidence, 3 of 4 guidelines (3 good quality, 1 fair quality) recommended against the use of HBOT as adjunct treatment in the management of pressure ulcers because of insufficient evidence. Despite the lack of supporting evidence, the Registered Nurses' Association of Ontario recommended that HBOT be considered for the management of pressure ulcers, basing their recommendation on expert opinion and consensus. Fair-quality guidelines on the management of lower extremity amputations from the VA and DOD are consistent with the evidence, whereas the Wound, Ostomy and Continence Nurses Society (2008) recommended that HBOT be considered for lower extremity arterial ulcers for which there is little evidence (fair-quality guideline).

Late radiation tissue injury (LRTI): The Dutch Head and Neck Oncology Cooperative Group (2007) recommended HBOT for the treatment of osteoradionecrosis (ORN) of the mandible (fair-quality guideline).

Cerebral palsy: Also consistent with the evidence, the Canadian agency AETMIS recommended against the use of HBOT for cerebral palsy (fair-quality guideline).

Sensorineural hearing loss: The most recent good-quality guideline was a 2012 guideline from the American Academy of Otolaryngology – Head and Neck Surgery recommending the use of HBOT for the treatment of sensorineural hearing loss among patients presenting within 2 months of onset. The panel reasoned that the level of evidence for hearing improvement, albeit modest and imprecise, was sufficient to promote greater awareness of HBOT as an intervention for sudden sensorineural hearing loss.

Critically ill patients: One systematic review examining the use of HBOT for critically ill intubated, mechanically ventilated patients provided guidelines on the safe use of the technology for that population and for the personnel involved (poor-quality guideline) (Weaver, 2011).

SELECTED PAYER POLICIES

At the direction of Washington State HCA, the coverage policies for the following organizations were reviewed:

Centers for Medicare & Medicaid Services (CMS)

CMS covers HBOT administered in either a monoplace or multi-chamber for a number of indications. Covered conditions include the following (for a complete picture, we included all conditions covered by CMS in relation to HBOT irrespective of whether they were the focus of this report):

- Acute carbon monoxide intoxication.
- Decompression illness.
- Gas embolism.
- Gas gangrene.
- Acute traumatic peripheral ischemia. HBOT is a valuable adjunctive treatment to be used in combination with accepted standard therapeutic measures when loss of function, limb, or life is threatened.
- Crush injuries and suturing of severed limbs. As in the previous conditions, HBOT would be an adjunctive treatment when loss of function, limb, or life is threatened.
- Progressive necrotizing infections (necrotizing fasciitis).
- Acute peripheral arterial insufficiency.
- Preparation and preservation of compromised skin grafts (not for primary management of wounds).
- Chronic refractory osteomyelitis, unresponsive to conventional medical and surgical management.
- ORN as an adjunct to conventional treatment.
- Soft tissue radionecrosis as an adjunct to conventional treatment.
- Cyanide poisoning.
- Actinomycosis, only as an adjunct to conventional therapy when the disease process is refractory to antibiotics and surgical treatment.
- Diabetic wounds of the lower extremities in patients who meet the following three criteria:
  - Patient has type 1 or type 2 diabetes and has a lower extremity wound that is due to diabetes.
  - Patient has a wound classified as Wagner grade III or higher.
  - Patient has failed an adequate course of standard wound therapy.

The use of HBOT is covered as adjunctive therapy only after there are no measurable signs of healing for at least 30 days of treatment with standard wound therapy and must be used in addition to standard wound care. Standard wound care in patients with diabetic wounds includes: assessment of a patient's vascular status and correction of any vascular problems in the affected limb if possible; optimization of nutritional status; optimization of glucose control; debridement by any means to remove devitalized tissue; maintenance of a clean, moist bed of granulation tissue with appropriate moist dressings, appropriate off-loading, and necessary treatment to resolve any infection that might be present. Failure to respond to standard wound care occurs when there are no measurable signs of healing for at least 30 consecutive days. Wounds must be evaluated at least every 30 days during administration of HBOT.

Continued treatment with HBOT is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment. All other indications not specified above are not covered under the Medicare program. No program payment may be made for any conditions other than those listed above. No program payment may be made for HBOT in the treatment of the following conditions:

- Cutaneous, decubitus, and stasis ulcers.
- Chronic peripheral vascular insufficiency.
- Anaerobic septicemia and infection other than clostridial.
- Skin burns (thermal).
- Senility.
- Myocardial infarction.
- Cardiogenic shock.
- Sickle cell anemia.
- Acute thermal and chemical pulmonary damage, i.e., smoke inhalation with pulmonary insufficiency.
- Acute or chronic cerebral vascular insufficiency.
- Hepatic necrosis.
- Aerobic septicemia.
- Nonvascular causes of chronic brain syndrome (Pick's disease, Alzheimer's disease, Korsakoff's disease).
- Tetanus.
- Systemic aerobic infection.
- Organ transplantation.
- Organ storage.
- Pulmonary emphysema.
- Exceptional blood loss anemia.
- Multiple sclerosis.
- Arthritic diseases.
- Acute cerebral edema.

Since HBOT for the treatment of sensorineural hearing loss, TBI, other brain injuries, and cerebral palsy do not appear on the list of covered conditions, we can assume that there is no reimbursement coverage for these conditions (CMS, 2012).

Aetna

Aetna considers systemic HBOT medically necessary for any of the following conditions (Aetna, 2012):

- Acute air or gas embolism.
- Acute carbon monoxide poisoning.
- Acute cerebral edema.
- Acute peripheral arterial insufficiency (i.e., compartment syndrome).
- Acute traumatic peripheral ischemia (including crush injuries and suturing of severed limbs) when loss of function, limb, or life is threatened and HBOT is used in combination with standard therapy.

- Chronic refractory osteomyelitis, unresponsive to conventional medical and surgical management.
- Compromised skin grafts and flaps.
- Cyanide poisoning (with coexisting carbon monoxide poisoning).
- Decompression illness ("the bends").
- Exceptional blood loss anemia only when there is overwhelming blood loss and transfusion is impossible because there is no suitable blood available, or religion does not permit transfusions.
- Gas gangrene (clostridial myositis and myonecrosis).
- Idiopathic sudden deafness, acoustic trauma or noise-induced hearing loss, when HBOT is initiated within 3 months after onset.
- Nonhealing infected deep ulcerations (reaching tendons or bone) of the lower extremity in diabetic adults unresponsive to at least 1 month of meticulous wound care. Standard wound care in persons with diabetic wound includes (i) assessment of vascular status and correction of any vascular problems in the affected limb if possible, (ii) optimization of nutritional status, (iii) optimization of glucose control, (iv) debridement by any means to remove devitalized tissue, (v) maintenance of clean, moist bed of granulation tissue with appropriated moist dressings, (vi) appropriate off-loading, and (vii) necessary treatment to resolve any infection that might be present. Failure to respond to standard wound care occurs when there are no measurable signs of healing for at least 30 consecutive days. Wounds must be evaluated at least every 30 days during the administration of HBOT. Continued treatment with HBOT is not considered medically necessary if measurable signs of healing have not been demonstrated within any 30-day period of treatment. NOTE: HBOT is not considered medically necessary for superficial lesions.
- Pneumatosis cystoides intestinalis.
- Progressive necrotizing soft tissue infections, including mixed aerobic and anaerobic infections (Meleney's ulcer, necrotizing fasciitis).
- Prophylactic pretreatment and posttreatment for members undergoing dental surgery of a radiated jaw.
- Radiation-induced hemorrhagic cystitis.
- Radiation necrosis (brain radionecrosis, myoradionecrosis, ORN, and other soft tissue radiation necrosis).
- Radiation proctitis.

Aetna considers the use of systemic HBOT experimental and investigational for the following conditions relevant to this report because there is insufficient evidence in the medical literature establishing that systemic HBOT is more effective than conventional therapies:

- Acute renal arterial insufficiency.
- Acute thermal and chemical pulmonary damage, i.e., smoke inhalation (e.g., carbon tetrachloride, hydrogen sulfide) with pulmonary insufficiency.
- Aerobic septicemia and systemic aerobic infection.
- Anaerobic septicemia and infection other than clostridial.
- Anoxic brain injury.
- Aseptic necrosis of the femoral head and neck.
- Bone grafts or fracture healing (e.g., nonunion fractures).

- Cerebral palsy.
- Chronic peripheral vascular insufficiency.
- Closed head and/or spinal cord injury.
- Cognitive impairment (e.g., senility, senile dementia).
- Diabetic superficial wounds.
- Migraine or cluster headaches.
- Multiple sclerosis.
- Noncompromised skin grafts and flaps.
- Nondiabetic cutaneous, decubitus, pressure and venous stasis ulcers.
- Nonvascular causes of chronic brain syndrome (e.g., Alzheimer's disease, Korsakoff's disease, Pick's disease).
- ORN of the jaw.
- Radiation-induced cholangitis, myelitis, enteritis.
- Recto-vaginal fistula.
- Skin burns (thermal).
- Superficial and/or noninfected diabetic ulcers.
- Surgical wound dehiscence.

Aetna considers systemic HBOT experimental and investigational for members with any of the following contraindications to systemic HBOT, as the safety of systemic HBOT for persons with these contraindications to HBOT has not been established:

- Concurrent administration of doxorubicin, cisplatin, or disulfiram
- Premature infants (birth prior to 37 weeks gestation)
- Untreated pneumothorax

Regence BCBS

Topical hyperbaric and topical normobaric oxygen therapy is considered investigational and is not covered by Regence BCBS. Systemic HBOT must comply with the following guidelines, which are consistent with the Undersea and Hyperbaric Medical Society criteria (Regence BCBS, 2011):

- Patients must breathe 100% oxygen intermittently or continuously while the pressure of the treatment chamber is increased above 1 atmosphere absolute (ATA).
- Systemic hyperbaric oxygen pressurization should be at least 1.4 ATA (20.5 pounds per square inch [psi]).
- Treatment is provided in a hospital or clinic setting.

Oxygen therapy that does not meet the above criteria is considered investigational, including, but not limited to, the following:

- Mild hyperbaric oxygen chambers (< 1.4 ATA/20.5 psi)
- In-home hyperbaric oxygen therapy

Systemic hyperbaric oxygen pressurization (i.e., 100% oxygen delivered within a chamber at a pressure of at least 1.4 ATA) may be considered medically necessary in the treatment of the following conditions:

Acute carbon monoxide poisoning.

- Acute traumatic ischemia (i.e., reperfusion injury, crush injury, compartment syndrome).
- Chronic refractory osteomyelitis.
- Cyanide poisoning, acute.
- Decompression sickness.
- Gas or air embolism, acute.
- Gas gangrene (i.e., clostridial myositis and myonecrosis).
- Nonhealing diabetic wounds of the lower extremities as an adjunct to ongoing conventional wound care in patients who meet **all** of the following 3 criteria:
  - Patient has type 1 or 2 diabetes and has a lower extremity wound that is due to diabetes.
  - Patient has a wound classified as Wagner grade 3 or higher.
  - Patient has no measurable signs of healing after 30 days of an adequate course of standard wound therapy, including **all** of the following:
    A. Assessment of vascular status and correction of any vascular problems in the affected limb if possible.
    B. Optimal glycemic control.
    C. Optimal nutritional status.
    D. Topical wound treatment (e.g., saline, hydrogels, hydrocolloids, alginates) with maintenance of a clean, moist bed of granulation tissue.
    E. Debridement to remove devitalized tissue, any technique.
    F. Pressure reduction or offloading.
    G. Treatment to resolve infection (e.g., antibiotics).
- Pretreatment and posttreatment for patients undergoing dental surgery (non–implant-related) of an irradiated jaw.
- Profound anemia with exceptional blood loss (only when blood transfusion is impossible or must be delayed).
- Soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis) and ORN.

Hyperbaric oxygen pressurization is considered investigational for all other indications, including the following conditions relevant to this review:

- Acute arterial peripheral insufficiency.
- Acute osteomyelitis, refractory to standard medical management.
- Acute thermal burns.
- Bone grafts.
- Cerebral palsy.
- Compromised skin grafts or flaps.
- Demyelinating diseases, e.g., multiple sclerosis, amyotrophic lateral sclerosis.
- Early treatment (beginning at completion of radiation therapy) to reduce adverse effects of radiation therapy.
- Femoral neck necrosis, idiopathic.
- Fracture healing and fracture nonunion treatment.
- Headache prevention and/or treatment of symptoms, including, but not limited to, migraine and cluster headaches.

- Idiopathic sudden sensorineural hearing loss.
- Necrotizing soft tissue infections.
- Retinal artery insufficiency, acute.
- Traumatic brain injury.
- Acute surgical wounds.
- Arterial insufficiency ulcers.
- Decubitus ulcers.
- Nondiabetic cutaneous ulcers.
- Noninfected wounds (Wagner grade I or II).
- Pressure sores.
- Ulcers caused by atherosclerotic vascular disease.
- Ulcers caused by peripheral vascular disease.
- Venous stasis ulcers.

Group Health Cooperative

Group Health covers HBOT for members with the following conditions (GroupHealth, 2010):

- Acute carbon monoxide intoxication.
- Decompression illness.
- Gas embolism.
- Gas gangrene.
- Acute traumatic peripheral ischemia in combination with accepted standard therapeutic measures, when loss of function, limb, or life is threatened.
- Crush injuries and suturing of severed limbs as above in combination with accepted standard therapeutic measures, when loss of function, limb, or life is threatened.
- Progressive necrotizing infections (necrotizing fasciitis).
- Acute peripheral arterial insufficiency.
- Treatment of compromised skin grafts, excludes artificial skin graft.
- Chronic refractory osteomyelitis, unresponsive to conventional medical surgical treatment.
- Osteoradionecrosis as an adjunct to conventional treatment.
- History of previous radiation therapy to the mandible or maxilla of 5 to 7000 rads.
- Soft tissue radionecrosis as an adjunct to conventional treatment.
- Cyanide poisoning.
- Actinomycosis only as an adjunct to conventional therapy when disease process is refractory to antibiotics and surgery.
- Diabetic wounds of the lower extremities in patients who meet all of the following criteria:
  - Patient has type 1 or type 2 diabetes and has a lower extremity wound that is due to diabetes.
  - Patient has a wound classified as Wagner grade III or higher.
  - Patient has failed an adequate course of standard wound therapy (no measurable healing after 30 days of treatment).

Continued therapy after 30 days is only covered if measurable signs of healing have not been demonstrated. Therapy must be provided to the entire body under increased atmospheric pressure—never topically. Therapy must be provided in an environment that has constant hyperbaric physician

supervision. Group Health does not cover the following indications relevant to this report (the list is not exhaustive of all exclusions):

- Cutaneous, decubitus, and stasis ulcers.
- Chronic peripheral vascular insufficiency.
- Anaerobic septicemia and infection, other than clostridial.
- Skin burns (thermal).
- Acute thermal and chemical pulmonary damage, i.e., smoke inhalation and pulmonary insufficiency.
- Acute or chronic cerebral vascular insufficiency.
- Hepatic necrosis.
- Aerobic septicemia.
- Nonvascular causes of chronic brain syndrome (Pick's disease, Alzheimer's disease, Korsakoff's disease).
- Tetanus.
- Systemic aerobic infection.
- Multiple sclerosis.

Summary: Payer policies

Reimbursement policies among the four agencies examined (CMS, Aetna, Regence BCBS, and Group Health) generally reflect the findings of this report. Conditions that have at least moderate-quality evidence supporting the efficacy and safety of HBOT are covered by most if not all agencies. Conditions with moderate-quality evidence showing no benefit to HBOT are not covered, and agencies are split over those conditions where the evidence conflicts, is weak, or insufficient. For example, all of the agencies cover the use of HBOT for the management of diabetic nonhealing wounds, including foot ulcers (using similar definitions for the category of nonhealing wound), refractory osteomyelitis, ORN, and soft tissue radionecrosis. Three of four also cover crush injuries, compromised skin grafts, and peripheral arterial insufficiency. None offer coverage for HBOT as a treatment for headaches/migraine, thermal burns, brain injury, cerebral palsy, or multiple sclerosis. One group (Aetna) offers coverage for sensorineural hearing loss; one does not cover compromised skin grafts (Regence BCBS) and one does not cover peripheral arterial insufficiency (Regence BCBS).

OVERALL SUMMARY AND POLICY CONSIDERATIONS

Evidence-Based Conclusions

The volume of evidence demonstrates an active research field examining the use of HBOT to treat a wide variety of indications. There have been several good-quality systematic reviews published in the last 10 years, some of which provide moderate-quality evidence of the effectiveness and harms associated with HBOT. However, the current evidence remains insufficient to definitively answer questions of effectiveness in relation to a number of indications. Furthermore, there is little evidence on the optimal frequency, duration, and dose of treatment and little known about which subpopulations are likely to benefit most from treatment.

Indications for which there is moderate-quality evidence of the effectiveness of HBOT

Moderate-quality evidence supports the addition of HBOT to standard wound care to promote short-term wound healing and limb salvage among patients with diabetic foot ulcers. There is no evidence of improvement beyond 1 year, and there is insufficient evidence to determine the effect of HBOT on quality of life (QOL) or other health outcomes. There is also moderate-quality evidence suggesting that HBOT improves outcomes of LRTI affecting bone and soft tissues. There is no overall estimate of effect because of the heterogeneity between studies, but the evidence suggests that radiation-induced tissue and bone damage to the head and neck, anus, and rectum may benefit from HBOT. In addition, there is moderate-quality evidence that HBOT reduces the risk of developing ORN following tooth extraction in a previously irradiated area. Moderate-quality evidence also suggests that HBOT reduces the risk of dying following TBI, but there is little evidence that those who survive have a good functional outcome. Finally, moderate-quality evidence suggests that 40 to 45 minutes of HBOT is effective in significantly relieving an acute migraine attack, but there is no evidence that HBOT can prevent migraines, reduce the nausea and vomiting associated with migraines, or reduces the need for rescue medication.

Indications for which there is low-quality evidence of effectiveness of HBOT

There is limited low-quality evidence suggesting that HBOT may improve healing when employed as an adjunct treatment for venous ulcers, flaps and grafts, crush injuries, and surgical reconstruction (without grafts or flaps) but more study is needed to support the current evidence. Low-quality evidence (due to mixed results) is inconclusive as to whether or not there is a benefit of HBOT for the treatment of sensorineural hearing loss in the acute phase of the disease. A large systematic review suggests that HBOT is beneficial among patients who present within 2 weeks of onset; however, there is no evidence that the statistical benefit observed translates into a functional benefit, and the results from a recent RCT do not support that finding.. Low-quality evidence (because of poor study design) also suggests a possible benefit of HBOT as an adjunct treatment for refractory osteomyelitis, 1 small, fair-quality, nonrandomized trial suggests that HBOT may reduce the rates of relapse infection but further good-quality studies are necessary to confirm this finding. There is low-quality evidence suggesting that transcutaneous oxygen measurement (TCOM) can identify patients most likely to benefit from HBOT, as well as low-quality evidence suggesting that patients having received a radiation dose > 60 grays (Gy) for the treatment of head and neck cancer and requiring extraction of mandibular teeth within the radiated field may benefit more from HBOT than those having received a lower radiation dose.

Indications for which there is moderate-quality evidence of no effectiveness of HBOT

Moderate-quality evidence suggests little benefit of HBOT for the treatment of multiple sclerosis. Of note is that there were no RCTs found on this topic after 1990 and this application of HBOT does not appear to be an area of active investigation.

Indications for which there is low-quality evidence of no effectiveness of HBOT

Low-quality evidence suggests no benefit of HBOT for preventing, relieving, or terminating cluster headaches. There is also no evidence that HBOT is beneficial among patients presenting with chronic sensorineural hearing loss.

Findings for which there is insufficient evidence of effectiveness

There is insufficient evidence, primarily due to mixed results or an overall paucity of studies, to determine if HBOT is effective for the treatment of thermal burns, cerebral palsy, or brain injuries other than TBI.

Cost-Effectiveness

The available cost analyses are limited by sparse cost data and a wide range of efficacy estimates. Under the base case model assumptions employed in the included cost analyses, there is a low quality of evidence to suggest that HBOT may be cost effective or cost saving for the treatment of diabetic nonhealing wounds and the prevention of ORN. The base case assumptions and sensitivity parameters used as estimates for HBOT effectiveness were in line with the estimates found in this report and found to be of moderate quality. The results demonstrated cost-effectiveness under base case assumption but proved not to be robust when a range of parameters were examined during sensitivity analyses. Cost analyses for the use of HBOT for nondiabetic nonhealing wounds and burns also found HBOT to be cost effective under base case assumption but, once again, were very sensitive to the range of effectiveness parameters employed during sensitivity analyses, suggesting the models were not robust and therefore unreliable. In addition, we found the evidence supporting the use of HBOT for nondiabetic nonhealing wounds and burns to be of low and insufficient quality, respectively, indicating the need for further caution in interpreting the cost analyses for these indications. Overall there is a low quality of evidence to suggest that HBOT may be a cost-effective treatment under certain conditions and for certain populations and indications, but current data are insufficient to determine the most cost-effective uses of the technology.

Harms

There is moderate-quality evidence that harms associated with HBOT are usually mild and self-limiting, with most resolving after termination of treatment. The most common harms include myopia, barotrauma, claustrophobia, and oxygen toxicity. Life-threatening adverse events are rare but do occur on occasion and can include seizures and death. There is some evidence but of an unknown quality that comorbidities such as lung disease, previous ear surgery or trauma, significant upper respiratory infections, fever, claustrophobia, preexisting cataracts, optic neuritis, and pregnancy are contraindications for HBOT.

Key Gaps in the Evidence

On the question of the effectiveness of HBOT, no high-quality evidence was found for any of the indications under review. There was moderate-quality evidence for five indications (diabetic foot ulcers, LRTI, migraines, multiple sclerosis, and TBI) for at least one primary health outcome, while the body of evidence related to nonhealing nondiabetic wounds, refractory osteomyelitis, brain injuries other than TBI, cerebral palsy, sensorineural hearing loss, and headaches was found to be of low or very low quality overall. Future work needs to focus on designing methodologically rigorous studies, which are adequately powered, free from the risk of publication bias, and generalizable to the population of patients under review.

The question of optimal frequency, duration, and dose of treatment remains unanswered. Future studies need to address these questions specifically for each indication and for a variety of subpopulations. Similarly, this report is largely unable to answer the question of differential effectiveness. Currently, we do not know who is most likely to benefit from HBOT. Definitive patient selection criteria will remain limited until these questions are answered.

Cost data are limited because of the paucity of data already described. Robust models arising from more reliable cost and effectiveness data are necessary to determine the cost-effectiveness of HBOT for the various indications.

LIMITATIONS OF THIS REPORT

The following limitations apply to the methodology used for this report:

- To accommodate the evaluation of evidence for nine indications, this report relied primarily on the available data from other systematic reviews and health technology assessments (HTAs). We are confident that all relevant primary data studies were found using this methodology, but there is an increased risk of errors or missed data using such a format.
- Despite the breadth of indications covered in this report, hyperbaric oxygen therapy (HBOT) has been suggested as a novel treatment for several other nontraditional conditions, which are not covered in the current report. These include, but are not limited to, autism, Bell's palsy, compartment syndrome, stroke, acute coronary syndrome, fractures, ophthalmological conditions, and posttraumatic stress disorder (PTSD).

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APPENDICES

Appendix I. Search Strategy

Search Dates

PubMed, Cochrane library, CRD, and Embase searches were conducted on June 20, 2012. An update search of the MEDLINE and Embase databases was conducted on November 8, 2012. The update search was limited to RCTs and meta-analyses.

Search Strings

The PubMed search used the following MEDLINE MeSH description for Hyperbaric Oxygenation:

> "The therapeutic intermittent administration of **oxygen** in a chamber at greater than sea-level atmospheric pressures (three atmospheres). It is considered effective treatment for air and gas embolisms, smoke inhalation, acute carbon monoxide poisoning, caisson disease, clostridial gangrene, etc. (from *Dictionary of Modern Medicine*, 1992). The list of treatment modalities includes stroke."

PubMed Search: **"Hyperbaric Oxygenation"[Mesh]** Filters: **Published in the last 10 years; Humans; Practice Guideline; Systematic Reviews; Meta-Analysis; Review; English**

Embase, Cochrane library, and CRD searches: Hyperbaric Oxygen as text word

The above searches were combined with relevant keywords and MeSH terms from the following list of indications to identify studies published subsequent to the review(s) selected for each indication:

- Diabetic nonhealing wounds
- Diabetic foot ulcers
- Nonhealing wounds
- Skin and tissue graft
- Thermal burns
- Surgical wounds
- Refractory osteomyelitis
- Late radiation tissue injury (LRTI)
- Osteoradionecrosis
- Brain injury
- Traumatic brain injury
- Cerebral palsy
- Headache
- Migraine
- Multiple sclerosis
- Sensorineural hearing loss

Harms data: A specific search for harms data limited to the last 10 years but not limited to systematic reviews was conducted using the same search terms as outlined above.

Cost studies: The National Health Service Economic Evaluation Database as part of the UK Research Center for Reviews and Dissemination (NHS-CRD) was searched for economic evaluation. In addition, the following search string was used in PubMed to identify **economic evaluation and cost-specific studies**:

> ((((economic analysis) OR (economic evaluation)))) OR (((((cost AND (analysis OR benefit OR effective* OR consequence OR minimization)))) OR (("Costs and Cost Analysis"[MeSH] OR "Cost-Benefit Analysis"[MeSH])))) AND Hyperbaric Oxygenation"[Mesh].

Appendix II. Overview of Evidence Quality Assessment Methods

Tools used include the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Shea et al., 2007); internally developed Quality Checklists for evaluating the quality (internal validity) of different types of studies, and the Hayes Grading Guides for evaluating bodies of evidence for different types of technologies, which is in alignment with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, developed by the international collaborative GRADE Working Group.

Step 1	Systematic review appraisal a. Rate the quality of each systematic review using the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Shea et al., 2007). This step is only necessary when data synthesis such as meta analysis is conducted within the review and used in addition to or in place of individual study data
Step 2	Individual study appraisal a. Initial rating according to study design *Good:* Randomized Controlled Trials *Fair:* Nonrandomized Trial (controlled, parallel group, quasi-randomized) *Poor:* Observational Analytic Studies (prospective or retrospective trials involving historical controls, pretest posttest control trial [patients legitimately serve as their own controls], case-control, registry/chart/database analysis involving a comparison group) *Very Poor:* Descriptive Uncontrolled Studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data]) b. Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist c. Repeat for each study
Step 3	Evaluation of each body of evidence by outcome, key question, or indication a. Initial quality designation according to *best* study design in a body of evidence b. Downgrade/upgrade *Downgrade factors:* Study weaknesses (Quality Checklists), lack of applicability, inconsistency of results, small quantity of data, publication bias (if adequate information is available) *Possible upgrade factors:* Strong association, dose-response effect, bias favoring no effect c. Assign final rating: High-Moderate-Low-Very Low d. Repeat for each outcome/question/application
Step 4	Evaluation of overall evidence a. Rank outcomes by clinical importance b. Consider overall quality of the evidence for each *critical* outcome c. Assign overall rating based on lowest-quality body: High-Moderate-Low-Insufficient
Step 5	Evidence-based conclusion Overall quality of the evidence + balance of benefits and harms

Appendix III. Summary of Key Findings from Systematic Reviews

KQ1, KQ1a, KQ2, and KQ3

Because of the overlap in studies answering KQ1, KQ1a, KQ2, and KQ3, we present summary tables for these key questions by indication and in alphabetical followed by chronological arrangement.

Key: ADL, activities of daily living; AE, adverse events; AHA, American Heart Association; AHRQ, Agency for Healthcare Research and Quality; ATA, atmosphere absolute; BP, blood pressure; CBF, cerebral blood flow; CENTRAL, Cochrane Central Register of Controlled Trials; CFL, cerebrospinal fluid lactate; CI, confidence interval; CMRO2, cerebral metabolic rate of O2; CNS, central nervous system; CP, cerebral palsy; CT, computed tomography; dB, decibel(s); DORCTHIM, Database of Randomized Controlled Trials in Hyperbaric Medicine; EDSS, Expanded Disability Status Scale; FSS, Functional Status Score; f/u, follow-up; GCS, Glasgow Coma Scale; GMFM, Gross Motor Function Measure; grp(s), group(s); Gy, gray; HA, hyaluronic acid; HBOT, hyperbaric oxygen therapy; H&N, head and neck; HR, heart rate; HTA, health technology assessment; hx, history; ICP, intracranial pressure; ISSHL, idiopathic sudden sensorineural hearing loss; ITT, Intention-to-treat; LENT-SOMA, Late Effects Normal Tissue-Subjective, Objective, Management, Analytical; LNNB, Luria-Nebraska neuropsychological battery; LRTI, late radiation tissue injury; MANTIS, Manual Alternative and Natural Therapy Index System; MD, mean difference; MEBT, middle ear barotrauma; Misc, miscellaneous; mm Hg, millimeter of mercury; MS, multiple sclerosis; MSAC, Medical Services Advisory Committee; NBH, normobaric hyperoxia; NNT, number needed to treat; NR, not reported; OR, odds ratio; ORN, osteoradionecrosis; PaO_2, arterial oxygenation; PEDI, Pediatric Evaluation of Disabilities Inventory; PEDro, Physiotherapy Evidence Database; PIN_2, partial pressure of inspired nitrogen; PIO_2,. partial pressure of inspired oxygen; postop; postoperative; preop, preoperative; PTA, pure tone average; pts, patients; QOL, quality of life; RCT, randomized controlled trial; RR, relative risk; sig, significant; SR, systematic review; std, standard; STEER, Succinct and Timely Evaluated Evidence Review; sx, symptom(s); TBI, traumatic brain injury; TCOM, transcutaneous oxygen measurement; tx, treatment (or therapy); tx'd, treated; USPSTF, U.S. Preventive Services Task Force; VAS, visual analog scale; WeeFIM, Functional Independence Measure for Children; WMD, weighted mean difference

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
Diabetic Wounds					
Goldman (2009) (diabetic wounds) Systematic review and meta-analysis to evaluate the evidence of the efficacy of HBOT for wound healing and limb salvage of	*Included studies:* Diabetic foot ulcers: 10 *Search strategy:* 1978-2008 *Data sources:* Ovid MEDLINE for RCTs, cohort studies, time series, and case series	Diabetic foot ulcers *Study design* n=10 (4 RCTs, 3 prospective cohorts, 2 retrospective cohorts and 1 case series) *Total sample size*	*HBOT dose (range)* 2.2-3.0 ATA, 45-120 mins, 4-101 sessions *Primary outcomes:* Amputation (7 studies), healing (6 studies)	<u>*Meta-analysis*</u> *Amputations* OR (95% CI): 0.242 (0.137-0.428) *Healing* OR (95% CI): 9.992 (3.972-25.132) <u>*Primary data*</u>	*Authors Conclusions* HBOT promotes limb salvage and healing for pts w/ diabetic foot ulcers. *Limitations* Inconsistencies between described methods and included studies;

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
diabetic foot ulcer Baroni et al. (1987) Oriani et al. (1990a) Doctor et al. (1992) Faglia et al. (1996) Zamboni et al. (1997) Faglia et al. (1998) Kalani et al. (2002) Abidia et al. (2003) Kessler et al. (2003) Fife et al. (2002)	*Inclusion criteria:* Human studies, including HBOT and wound healing *Exclusion criteria:* Retrospective uncontrolled trials; <5 participants; central nervous system conditions; late effects of radiation; acute wounds associated w/ multiple trauma and critical care, including necrotizing fasciitis and crush injury *Quality assessment:* Based on GRADE criteria	*(range)* 1055 (10-641) *Study quality* 3 high, 5 moderate, 2 low *Setting* 7 Europe, 2 U.S., 1 India *Age* Range 40-80 *HBA1c* Range 6.9-8.9 *Wagner score* Range I-IV		Baroni et al. (1987) *Amputation:* HBOT 11%, non-HBOT 40%, *P*<0.001 *Healing (closure)* HBOT 89%, non-HBOT 10%, *P*<0.001 Doctor et al. (1992) RCT *Amputation*: HBOT 13%, control 47% *P*<0.0 Oriani et al. (1990a) *Amputation:* HBOT 5%, non-HBOT 33%, *P*<0.001 Faglia et al. (1996) RCT *Amputation:* HBOT 9%, control 33% *P*=0.002 Zamboni et al. (1997) *Healing:* HBOT resulted in significant healing at end of each 7-wk tx period (*P*<0.05) Faglia et al. (1998) *Amputation:* HBOT 14%, non-HBOT 31% *P*=0.012 Kalani et al. (2002) *Amputation:* HBOT 12%, non-HBOT 33% NS *Healing (closure)* HBOT 76%, non-HBOT 48% NS Abidia et al. (2003) RCT *Amputation:* HBOT 11%, control 11% *Complete Healing* (1-yr post HBOT): HBOT 63%, control, 0% (*P*=0.027) Kessler et al. (2003) RCT Healing (day 30): HBOT 48%, control 41% (NS) *HBOT helped healing (%)* Wagner II: 84% Wagner III: 77% Wagner IV: 64% Wagner V: 28% <u>*Harms*</u> Ear barotrauma (n=1) Cataract (n=1)	individual study quality was rated higher in this review than other high quality reviews w/ the same included studies; several inconsistencies between data reported in tables and text; poor quality studies were included in meta-analysis, meta-analysis may have been inappropriate for these studies due to heterogeneity. *Quality of review* Poor
Kranke et al. (2012)	*Included studies*: 9	*Study design*	*HBOT dose (range)* 2.0-	**Diabetic nonhealing wounds:** *Meta-analysis*	*Author's conclusions*

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
Cochrane Collaboration A systematic review to assess the evidence for the benefits and harms of HBOT for the tx of chronic wounds **Diabetic nonhealing wounds** Abidia et al. (2003) (n=18) Doctor et al. (1992) (n=30) Duzgun et al. (2008) (n=100) Faglia et al. (1996) (n=70) Kessler et al. (2003) (n=28) Lin et al. (2001) (n=29) Löndahl et al. (2010) (n=94) Wang et al. (2011) (n=86) **Other nonhealing wounds** Hammarlund and Sundberg (1994) (n=16)	Diabetic foot ulcers: 8 Venous ulcers: 1 *Search strategy:* Update of a 2003 Cochrane Review *Search dates*: Up to January 2012 *Data sources:* Cochrane library, Ovid MEDLINE, EBSCO CINAHL; manually searched bibliographies for additional eligible trials; unpublished data sought *Inclusion criteria:* RCTs comparing the effect on chronic wound healing of HBOT vs non-HBOT tx; humans in any setting w/ a chronic nonhealing wound associated w/ venous or arterial disease, diabetes mellitus or external pressure; failed tx w/ alternative therapies; HBOT administered in compression chamber from 1.5-3.0 ATA, from 30-120 mins daily or twice daily; any standard tx comparator	9 RCTs, 1 protocol identified for future update (O' Reilly 2011) *Sample size* Diabetic foot ulcers: 455 (range 18-100) Other wounds: 16 *# HBOT sessions* Abidia et al. (2003): 30 Doctor et al. (1992): 4 Duzgun et al. (2008): NR Faglia et al. (1996): 39 Hammarlund and Sundberg (1994): 30 Kessler et al. (2003): 20 Lin et al. (2001): 30 Löndahl et al. (2010): 40 Wang et al. (2011): 20 *Comparators* Diabetic foot ulcers HBOT vs control: 7 HBOT vs extracorporeal shockwave tx:1	3.0 ATA, 45-120 mins, 4-40 sessions *Primary outcomes* Proportion of ulcers healed; proportion of pts undergoing amputation *Secondary outcomes* Time to healing; wound size reductions, QOL; pain, transcutaneous oxygen tensions and recurrence rate *Harms* % pts w/ visual disturbances; barotrauma; oxygen toxicity; any other adverse event	*Proportion of ulcers healed at 6 wks:* (Abidia 2003, Kessler 2003, Löndahl 2010) RR 5.2 (95% CI 1.25-21.66), I^2=0%, *P*=0.02 *Proportion of ulcers healed at 6 mos*: (Abidia 2003, Löndahl 2010) RR 1.70 (95% CI 0.9-3.2), I^2=0%, *P*=0.1 *Proportion of ulcers healed at 1 yr:* (Abidia 2003, Duzgun 2008, Löndahl 2010) RR 9.53 (95% CI 0.44-207.76), I^2=85%, *P*=0.15 *Proportion of participants requiring major amputation:* (Doctor 1992 at discharge, Faglia 1996 [7 wks], Abidia 2003 [1 yr], Löndahl 2010 [1 yr]) Risk ratio 0.36 (95% CI 0.11-0.18), I^2=50%, *P*=0.08 *Proportion of participants requiring minor amputation:* (Doctor 1992, Abidia 2003, Duzgun 2008, Löndahl 2010) Risk ratio 0.76 (95% CI 0.19-3.10), I^2=70%, *P*=0.71 Wound size reduction: 1 trial (Kessler 2003) reported a 41.8% reduction in HBOT grp vs 21.7% in control grp at 2 wks (*P*=0.04); no MD at 4 wks (48.1% vs 41.7%, MD 6.4%, 95% CI –15.3-28.1, *P*=0.56) *QOL* 1 trial (Löndahl 2010) reported no difference in overall physical summary scores between grps at 1-yr f/u (MD -0.2, 95% CI -8.58-8.18, *P*=0.96) and no difference in overall mental summary scores	Diabetic foot ulcers: There is some evidence that the addition of HBOT tx to standard wound care results in a significant improvement in wound healing by 6 wks but the improvement is not evident beyond 12-mos; HBOT does not appear to improve minor amputation rate; a potentially important effect on the rate of major amputation cannot be confirmed by this review. Venous ulcers: Insufficient evidence to draw adequate conclusions. *Limitations* Some studies may have been underpowered to find a statistically significant effect; possibility of clinical heterogeneity due to differential wound size or severity across studies (see I^2); overall patient inclusion criteria were not standard across

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
	Quality assessment: Based on Cochrane risk of bias criteria	Venous ulcers: Comparator tx not specified *F/u* Diabetic foot ulcers: Varied from immediately posttx to 22 mos posttx Venous ulcers: 18 wks *Risk of bias* Only 1 study (Löndahl 2010) received an overall low risk of bias. 4 studies had high risk of attrition bias (Abidia 2003, Faglia 1996, Kessler 2003, Wang 2011); 1 study had high risk of bias for the domain of participant blinding (Wang 2011), 8 studies had poor reporting introducing an unclear risk of bias for many domains		(MD 6.60, 95% CI -3.93-17.13, *P*=0.22) **Other nonhealing wounds** Hammarlund and Sundberg (1994) found a significant reduction in venous wound area at 6 wks (MD 33, 95% CI 18.97-47.03; *P*<0.00001); no difference at 18-wk f/u (MD 29.6%, 95% CI -23-82.2, *P*=0.27) and no significant difference in proportion of ulcers healed at any time; no data on arterial or pressure wounds <u>*Harms*</u> 2 trials stated explicitly that there were no complications (Doctor 1992, Abidia 2003); Kessler 2003 reported 1 barotrauma and Löndahl 2010 reported 2 persons removed due to claustrophobia; no harms reported in other trials	trials; controls poorly described and not standard; overall poor reporting suggests a high risk of bias is possible. *Quality of review* Good
Wang et al. (2003) CMS/AHRQ	*Included studies*: 31 (57 reported but 2 indications were not of interest to this	*Study design* 9 RCTs, 6 nonrandomized	HBOT employed as an adjunct therapy in all 31 included studies	**Acute traumatic peripheral ischemia** 1 case series (n=23) (Mathieu 1990); all pts receiving HBOT tx had improved wound recovery	*Author's conclusions* HBOT appears to aid in wound healing for

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
HTA to determine if HBOT tx is an effective adjunct tx for hypoxic wounds **Diabetic nonhealing wounds** Baroni et al. (1987) Oriani et al. (1990a) Wattel et al. (1990) Wattel et al. (1991) Doctor et al. (1992) Faglia et al. (1996) Zamboni et al. (1997) Faglia et al. (1998) **Chronic nonhealing wounds** (nondiabetic) Hammarlund and Sundberg (1994) **Acute traumatic peripheral ischemia** Mathieu et al. (1990) **Crush injuries and suturing of severed limbs** Bouachour et al. (1996) **Compromised skin**	review) *Search dates:* 1998 to August 2001 *Data sources:* MEDLINE and studies suggested by expert reviewers *Inclusion criteria*: RCTS, nonrandomized comparison studies, and case series; human subject studies; English-language; sample size ≥5 *Exclusion criteria:* Animal studies; conference proceedings w/o primary data; review articles *Quality Assessment* : NR	comparison studies, 16 case series *Sample size* 2070 (range 6-160) *Type of wound* Diabetic nonhealing wounds: 8 (2 RCTs, 4 nonrandomized controlled trials, 2 case series *Chronic nonhealing wounds (nondiabetic)* 1 RCT Acute traumatic peripheral ischemia: 1 case series Crush injuries and suturing of severed limb: 1 RCT Compromised skin grafts: 2 RCTs ORN: 3 (2 RCTs, 1 case series) Soft tissue radionecrosis: 13 case series	*HBOT dose (range)* 2-3.0 ATA, 45-120 mins *Primary outcomes* Mortality; amputation, wound healing; length of hospital stay; infection control, any other reported outcome *Harms:* any reported harms	and complete healing (no data presented) TCOM predicted the risk of amputation among pts breathing normal air, normobaric oxygen or hyperbaric oxygen **Crush injuries and suturing of severed limbs** 1 RCT (Bouachour 1996) (see Eskes 2010 for detailed results) found HBOT tx improved complete healing rates and reduced wound infection and wound dehiscence in crush injury **Compromised skin grafts** 2 RCTs, both reporting improved survival of skin grafts, wound infection, and complete wound healing w/ HBOT tx Perrins (1967): See Eskes 2010 for detailed results Marx (1994) (n=160): (not in Eskes 2010 review because the results appear in a book chapter) Wound infection, HBOT 6%, control 19%, RR 0.25 (NS); delayed wound healing, HBOT 11%, control 55%, RR 0.2 (95% CI NR), *P*=0.001 **ORN** 2 RCTs and 1 case series concluded that HBOT tx reduced the rate of ORN Marx (1985): See Bennett 2012 for detailed results Tobey (1979): Excluded from Bennett 2012 because full data was never published; results suggest that HBOT improved healing according to x-ray interpretation McKenzie (1993) (n=26): Case series; 81% improved, 50% had complete resolution of disease **Soft tissue radionecrosis** 13 case series all reporting a beneficial effect of	compromised skin grafts, ORN, soft tissue radionecrosis, and chronic nonhealing diabetic wounds; the literature provides no guidance on when HBOT tx should be initiated for chronic nonhealing wounds; no conclusions can be drawn on patient selection criteria; poor study design prevents any conclusions on whether tissue oxygen levels are a predictor of HBOT response. *Limitations* No formal assessment of risk of bias; 16 of 31 included studies were case series; poor reporting in the studies on crush injuries and ORN; poor quality data for soft tissue radionecrosis. *Quality of review* Fair

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
grafts Marx (1994) Perrins et al. (1967) **ORN** Marx et al. (1985) Tobey et al. (1979) McKenzie et al. (1993) **Soft tissue radionecrosis** Matthews et al. (1999) Woo et al. (1997) Warren et al. (1997) Neovius et al. (1997) Feldmeier et al. (1995) Bevers et al. (1995) Weiss et al. (1994) Norkool et al. (1993) Feldmeier et al. (1993) Williams et al. (1992) Nakada et al. (1992) Rijkmans et al. (1989) Ferguson et al. (1987) **Chronic refractory osteomyelitis** Esterhai et al. (1987) Davis et al. (1986)		Chronic refractory osteomyelitis: 2 (1 nonrandomized controlled trial, 1 case series) *# HBOT sessions (range)* 4-44 *Risk of bias* High overall		HBOT tx. One compared cases to historical controls and found a greater number of HBOT tx'd pts healed w/o surgical intervention. Complete healing (range across studies): 50%-100% **Chronic refractory osteomyelitis** 1 nonrandomized controlled trial and 1 case series were included. The nonrandomized controlled trial (Esterhai 1987) found HBOT tx had no effect on healing outcomes; the case series (Davis 1986) found that 89.5% of pts remained free of clinical signs of osteomyelitis for an average of 34 mos post HBOT. **Diabetic nonhealing wounds** 2 RCTs, 4 nonrandomized studies, and 2 case series. Overall authors found that HBOT tx significantly reduced wound size when compared w/ standard wound care alone and that HBOT was associated w/ a higher rate of complete healing as well as a decrease in major amputation rates. Faglia (1996) and Doctor (1992): See Kranke (2012) for a detailed description of results Faglia (1998) (n=115): Major amputation HBOT grp 14%, control 31%, *P*=0.01 Zamboni (1997) (n=10): Complete healing, HBOT grp 80%, control 20% (*P*<0.05) Baroni (1987) (n=28): Healing, HBOT grp 89%, control 10%, *P*=0.001; amputation, HBOT grp 11%, control 40%, *P*=0.01 Oriani (1990a) (n=80): "Recovery," HBOT grp 95%, control 67%, (*P*=NR); amputation, HBOT grp 5%, control 33%, *P*<0.001 Wattel (1990) (n=20 case series): Complete	

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
				healing, 75% Wattel (1991) (n=59 case series): Complete healing, 88% **Chronic nonhealing wounds (nondiabetic)** 1 RCT (Hammarlund and Sundberg 1994) found that HBOT significantly reduced wound surface area at 6 wks compared w/ controls (see Kranke 2012 for detailed results). Tissue oxygen level as a predictor of pt response to HBOT tx. A number of case series examined tissue oxygen levels and found tissue oxygen level to be a positive predictor of HBOT response. **Harms** 5 studies (of interest here) reported harms, including 1 case of minor blurring of vision; 2 transient vision changes; 3 pts requiring tympanostomy tubes; 1 case of barotrauma	
Other Nonhealing Wounds (not specific to diabetes)					
Eskes et al. (2010) Cochrane Collaboration A systematic review to determine the effects of HBOT on the healing of **acute surgical and traumatic wounds**	*Included studies:* 3 *Search dates:* Up to August 2010 *Data sources:* Cochrane library, Ovid MEDLINE, EBSCO CINAHL; manually searched bibliographies for additional eligible trials; unpublished data sought	*Study design* 3 RCTs *Sample size* 219 (range 36-135) *Type of wound* Bouachour (1996): crush injuries Perrins (1967): Split skin graft Xie and Li (2007):	*HBOT dose (range)* 2-2.5 ATA for 90-120 mins *Primary outcomes* Wound healing (e.g., time to healing, % healed) *Secondary outcomes* Survival of flap or graft, mortality, pain sores, QOL, pt satisfaction,	*HBOT vs usual care* (Perrins 1967) Graft survival (defined as 95% take):64% HBOT grp, 17% usual care grp (RR 3.5, 95% CI 1.35-9.11; NNT=2) *HBOT vs sham tx* (Bouachour 1996) Complete healing: HBOT grp 94%, sham grp 56% (RR 1.7 95% CI 1.11-2.61; NNT=3 *Time to healing* HBOT grp 50.2 (SD 21.1) days, sham grp 55.8 (19.9)	*Author's conclusions* Insufficient evidence to determine the effectiveness of HBOT tx on acute surgical or traumatic wounds. Limited evidence that HBOT may improve wound healing and reduce harms for crush injuries.

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
Bouachour et al. (1996) (n=36) Perrins (1967) (n=48) Xie and Li (2007) (n=135)	*Inclusion criteria:* RCTs recruiting people w/ acute wounds (e.g., surgical wounds, penetrating wounds, lacerations, skin transplantations, animal bites, traumatic wounds) *Exclusion criteria:* Open fractures and burns Eligible comparators: HBOT compared w/ any other intervention or sham HBOT; different HBOT regimens *Quality assessment:* Based on Cochrane risk of bias criteria	Flap grafting *# HBOT sessions* Bouachour 1996: 12 Perrins (1967): 5 Xie and Li (2007): 6-12 *Comparators* Bouachour (1996): Sham HBOT consisting of 21% O_2 at 1.1 ATA for 90 mins Perrins (1967): Usual care Xie and Li (2007): 2 comparators, dexamethasone or local injection of heparin *F/u* Bouachour (1996): NR Perrins (1967): 7 days Xie and Li (2007): 7 days *Risk of bias* Bouachour (1996): Unclear Perrins (1967): High Xie and Li (2007):	activities of daily living, $TcpO_2$ increase, major and minor amputations, length of hospital stay, costs *Harms* Visual disturbances, barotrauma, oxygen toxicity, infection, reoperations	days (MD -5.6 95% CI –19-7.8, not significant) *Amputation* HBOT grp 0, sham grp 2 (RR 0.2 95% CI 0.01-3.89, NS) Length of hospital stay: HBOT grp 22.4 (±12.4), sham grp 22.9 (±16.3) (MD –5.0 95% CI –9.96-8.96) NS *Harms* 2 additional surgical procedures (in 1 pt) in HBOT grp vs 8 in sham grp (RR 0.25 95% CI 0.06-1.02; NNT 3); necrotic tissue development, 1 in HBOT grp, 8 in sham grp (RR 0.13 95% CI 0.02-0.9; NNT=3) HBOT vs dexamethasone (Xie and Li, 2007) Complete survival of flap: HBOT grp 89%, dexamethasone 78% (RR 1.14, 95% CI 0.95-1.38, NS) HBOT vs heparin (Xie and Li, 2007) Complete survival of flap: HBOT 89%, heparin 73% (RR 1.21, 95% CI 0.99-1.49, NS)	*Limitations* Studies could not be pooled due to heterogeneity; unclear or high risk of bias prohibited drawing meaningful conclusions, many of the predefined secondary outcomes were not measured in the included studies. *Quality of review* Good

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
		High			
Garcia-Covrrubias et al. (2005) Tulane university A systematic review to evaluate the clinical experience w/ HBO in the management of **crush injuries and/or acute peripheral ischemia** Szekely et al. (1973) (n=5) No Authors (1975) (n=21) Monies-Chass et al. (1977) (n=7) Shupak et al. (1987) (n=13) Strauss and Hart (1989) (n=20) Radonic et al. (1995) (n=13) Bouachour et al. (1996) (n=36) Kiyoshige (1999) (n=6) Matos et al. (1999) (n=23)	*Included studies:* 9 *Search dates:* 1966-2003 *Data sources*: OVID MEDLINE and the Cochrane Library; review articles were manually searched for additional studies; meeting abstracts were included if they met inclusion criteria and were indexed in MEDLINE *Inclusion criteria:* Human studies w/ 5 or more participants; English language; sufficient information to evaluate HBOT regimen and clinical outcome *Quality assessment :* Instrument developed by the Eastern Association for the Surgery of Trauma (EAST) ad hoc committee on practice management guidelines	*Study design* 1 RCT, 8 case series *Sample size (range*) 5-36 *Type of wound* 6 studies w/ severe traumatic wounds, including crush injury; 2 studies of pts w/ amputated limbs, 1 study w/ compartment syndrome *# HBOT sessions* (range) 5-36 *Risk of bias* High	*HBOT dose (range)* 2-3 ATA for 60-120 mins *Outcomes* One poor-quality RCT (Bouachour, 1995) looked at complete healing, time to healing, amputations, length of stay in hospital and harms (see Eskes, 2010 for full description); outcomes not specified a priori for the case series	Only harms data abstracted because of the high risk of bias in the included studies <u>*Harms*</u> One serious complication mentioned but not specified	*Author's conclusions* Based on weak evidence, HBOT may be beneficial as an adjunct tx in acute traumatic ischemia and crush injury. Further well-designed studies are warranted. Few serious harms reported in included observational studies. *Limitations* Poor quality studies limiting the ability to draw meaningful conclusions; most studies failed to include a scoring system for the severity of the injury; protocols poorly described; harms poorly described. *Quality of review* Good

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
Goldman (2009) Systematic review and meta-analysis to evaluate the evidence of the efficacy of HBOT for wound healing and limb salvage in nonhealing wounds (not specific to diabetes) Efrati et al. (2007) (n=35) Saber et al. (2005) (n=35) Friedman et al. (2003) (n=6) Grolman et al. (2001) (n=36) Hammarlund and Sundberg (1994) (n=16) Reedy et al. (1994) (n=30) Mathieu et al. (1993) (n=15) Zhao et al. (1991) (n=54) Gonnering et al. (1986) (n=6)	*Included studies*:9 Arterial ulcers: 1 Leg ulcers: 2 Surgical reconstruction (w/o flaps or grafts): 2 Flaps and grafts: 4 *Search dates:* 1978-2008 *Data sources:* Ovid MEDLINE for RCTs, cohort studies, time series, and case series *Inclusion criteria:* Human studies, including HBOT and wound healing, HBOT and flaps and grafts *Exclusion criteria:* Retrospective uncontrolled trials; <5 participants; central nervous system conditions; late effects of radiation; acute wounds associated w/ multiple trauma and critical care, including necrotizing fasciitis and crush injury *Quality assessment:* Based on GRADE criteria	*Study design* 1 RCT, 1 prospective cohort, 1 retrospective cohort, 6 case series *Total sample size (range)* 194 (6-36) *Risk of bias* 1 high, 4 moderate, 4 low Age 42-81 (only reported for 5)	*HBOT dose (range)* 2.0-2.5 ATA, 90-120 mins, 7-190 sessions *Primary outcomes* Healing, amputation, successful flaps	<u>*Arterial ulcers*</u> Grolman et al. (2001) *Healing (# pts, %)* ΔTCOM >10 mm Hg: 19 (70%) ΔTCOM <10 mm Hg: 1 (11%) *P*<0.01 *Harms* 28%, anxiety, n=1; myopia, n=1; barotrauma, n=5; myringotomy, n=4; coronary heart failure, n=2; seizure, n=1 <u>*Leg ulcers*</u> Hammarlund and Sundberg (1994) *Healing (wound area reduction at 6 wks):* HBOT: 64% Control: 97% *P*<0.001 Efrati et al. (2007) *Healing (# pts, %)* *Complete healing:* 28 (80%) *Partial healing:* 4 (11%) *No improvement:* 3 (9%) *Harms* None <u>*Surgical reconstruction w/o flaps or grafts*</u> Zhao et al. (1991) *Improved wound healing:* HBOT: 89.2% Non-HBOT: 73.2% *P*<0.05	*Author's conclusions* HBOT may promote wound healing and graft take among pts w/ ulcers and undergoing surgical reconstruction. An increase of tissue O_2 tension of ≥10 torr when breathing pure O_2 suggests that the pt may benefit from HBOT. Those pts w/ an increase of <10 torr are unlikely to receive benefit from this tx modality. *Limitations* Dose not report results for 3 included studies; inconsistencies between described methods and included studies; individual study quality was rated moderate in a number of cases when it should have been low. *Quality of review* Poor

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				Breakdown and infection (# pts, %): Reedy et al. (1994) HBOT: 1 (17%) Non-HBOT: 7 (78%) *P*<0.01 <u>*Compromised flaps and grafts*</u> Saber et al. (2005) *Take at 18 mos f/u:* Complete take: 50% Partial take: 42% No take: 8% *Healing (# pts, %)* Mathieu et al. (1993) TCOM >50 mm Hg: 7 (100%) TCOM <50 mm Hg: 0 *P*<0.01 *Harms* None Gonnering et al. (1986) 100% survival Friedman et al. (2003) 100% composite graft take for all 6 pts receiving HBOT, graft did not take for 1 pt not receiving HBOT	
Villanueva et al. (2004) (search updated in June 2009; no additional eligible studies found)	*Included studies*: 2 *Search dates*: Up to June 2009 *Data sources:* Cochrane	*Study design* 2 RCTs *Sample size* 141 *Amount of body*	*HBOT dose* 2 ATA for 90 mins *Primary outcomes* Mortality rate, major morbidity rate (e.g., wound infection,	*Brannen (1997)* After adjusting for the pt's condition, there was no difference in length of hospital stay, mortality (11% in each grp), or # surgeries in HBOT and non-HBOT grps *Hart (1974)*	*Author's conclusions* Insufficient evidence to determine the effectiveness of HBOT for the management of thermal burns.

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Cochrane Collaboration A systematic review to assess the benefits of HBOT for the tx of thermal burns Brannen et al. (1997) (n=125) Hart et al. (1974) (n=16)	Library, MEDLINE, CINAHL; Embase, National Research Register, ISI Web of Science, DORCTHIM, text books, journals, conference proceedings, manually searched bibliographies for additional eligible trials; unpublished data sought *Inclusion criteria:* RCTs comparing HBOT w/ no HBOT for tx of pts w/ thermal injuries to the epidermis, subcutaneous tissues, vessels, nerve, tendons, or bone, all ages and both sexes Eligible comparators: Any standard regimes designed to promote burn healing *Quality assessment :* Based on Cochrane risk of bias criteria	*surface burned* Brannen (1997): NR Hart (1974): 10%-50% *Time from burn to hospital admittance* 24 hrs *# HBOT sessions* Brannen (1997): ≥10 Hart (1974): Every 8 hrs for 24 hrs then every 12 hrs until healed *Comparators* Usual care *Risk of bias* High	hemodynamic instability) *Secondary outcomes* Acute fluid requirement, time to healing, requirement for grafts and/or debridement, length of stay, scar quality, pain sores, activities of living *Harms* Visual disturbances, barotrauma, oxygen toxicity, any other reported harms	Mean time to healing HBOT: 19.7 days No HBOT: 43.8 days (P<0.001)	*Limitations* High risk of bias in both studies, studies could not be pooled due to heterogeneity; many of the outcomes of interest were not measured; very limited power in the Hart study and overall limited power to detect major harms; neither trial measured long-term outcomes. *Quality of review* Good
Refractory Osteomyelitis					
Hart (2012) Systematic review to evaluate the evidence of the efficacy of HBOT for	*Included studies*: 23 *Site of osteomyelitis* (# studies): 24 sites in 23 studies Long bone and misc sites:	*Study design* 2 prospective cohorts, 21 retrospective case series	*HBOT dose:* NR *# Sessions* Range 17-50 *Primary outcomes:*	**Long bone and misc osteomyelitis sites** **Overall** Antibiotics plus surgical debridement w/o HBOT provides cures in 70%-80% of refractory osteomyelitis cases; HBOT combined w/ antibiotics provides cures in 60%-70% of refractory	*Author's conclusions* While no RCTs exist, the overwhelming majority of published studies support HBOT as a safe and effective adjunct to

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
the tx of refractory osteomyelitis Ahmed et al. (2009) (n=6) Aitasalo et al. (1998) (n=33) Barili et al. (2007) (n=32) Bingham and Hart (1977) (n=70) Chen et al. (2004) (n=13) Chen et al. (2003) (n=14) Chen et al. (1998) (n=15) Chen et al. (2008) (n=10) Davis et al. (1986) (n=38) Davis et al. (1992) (n=16) Esterhai et al. (1987) (n=28) Higuchi et al. (2006) (n=4) Jamil et al. (2000) (n=16) Larsson et al. (1992) (n=36) Lentrodt et al. (2007) (n=3) Martel et al. (2000) (n=22)	10 Mandibular: 4 Spinal: 2 Cranial: 2 Malignant external otitis: 4 Sternal: 2 *Search dates*: 1965-2011 *Data sources:* NR *Inclusion criteria:* Human studies, including the terms HBOT and osteomyelitis; English language; original data *Exclusion criteria:* Literature reviews, mixed populations; studies n<3 *Quality assessment:* Based on AHA level of evidence criteria	*Sample size (range)* 505 (3-70) *Quality of studies* Good as assessed by author *Age* NR *Definition of refractory osteomyelitis* Generally defined as osteomyelitis failing to respond to definitive surgical debridement and a period of 2-4 wks of appropriate antibiotic tx *F/u* Range 3-84 mos	Resolution/cure, recurrence, drainage, hospital stay, duration of antibiotics	osteomyelitis cases; HBOT combined w/ antibiotics and surgical debridement provides cures in 80%-90% of refractory osteomyelitis cases **Esterhai (1987)** No benefit from adjunctive HBOT *Eradication of osteomyelitis:* HBOT grp: 79%, Non-HBOT grp: 93% *# recurrences:* HBOT grp 2, non-HBOT grp 1 **Perrins (1966)** *Overall cure rate:* 62% (complete healing: 79% [19/24]; improvement 8.3% [2/24], failure in 12.5% [3/24]; relapse 4 cases) **Bingham (1977)** Overall cure rate: 61% **Morrey (1979)** Disease free at 23 mos: 85% (34/40) **Davis (1986)** Infection free at 3 yrs F/u: 89% (34/38) **Maynor (1998)** Drainage-free at 3 mos: 82% (28/34) Drainage-free at 24 mos: 81% (21/24) Drainage-free at 60 mos: 80% (12/15 Drainage-free at 84 mos: 63% **Chen (2008)** Pts cured: 80% (8/10)	the management of refractory osteomyelitis; when used appropriately HBOT appears to reduce the total need for surgical procedures and antibiotic tx. *Comments* Contrary to the authors' conclusion, a reassessment of the quality of evidence suggests a low overall rating for the efficacy of HBOT as an adjunct for the tx of refractory osteomyelitis. *Limitations* Quality of evidence was rated good by the author based on AHA criteria, however 21/23 included studies were retrospective small case series w/ high risk of bias, the decision to determine a good overall quality of evidence ignores the serious methodological limitations to these studies, including a very high risk of selection and publication bias; overall

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Maynor et al. (1998) (n=34) Morrey et al. (1979) (n=40) Naronzy et al. (2006) (n=8) Perrins et al. (1966) (n=24) Sandner et al. (2009) (n=10) Tisch and Maier (2006) (n=22) Van Merkestyen et al. (1984) (n=16)				**Chen (2004)** Pts cured: 92% (12/13) # recurrences: 0 **Chen (2003)** Pts cured: 79% (11/14) **Chen (1998)** Pts cured: 87% (13/15) # recurrences: 0 Mandibular osteomyelitis **Overall** HBOT is not effective as a solitary tx for mandibular osteomyelitis; in adults tx w/ a combination of antibiotics, surgical debridement and HBOT is most effective; younger pts may also see effective results w/ a combination of HBOT and antibiotics w/o surgery **Aitasalo (1998)** Resolution w/ a combination of preop and postop HBOT plus antibiotics: 79% (26/33) Jamil (2000) Lasting resolution w/HBOT alone: 37% (6/16) **Lentrodt (2007)** Resolution w/ a combination of antibiotics and HBOT in younger pts: 100% (3/3) **Van Merkestyen (1984)** Cured w/ antibiotics and HBOT: 11% (1/9) Improvement w/ antibiotics, decortication and HBOT: 100% (7/7)	poor reporting of HBOT protocols w/ no info on HBOT dose. *Quality of review* Fair

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
				Spinal osteomyelitis **Overall** HBOT may be effective as an adjunct to antibiotics and, where indicated, limited surgical debridement among pts w/ spinal osteomyelitis **Ahmed (2009)** Resolution w/ a combination of antibiotics and HBOT (n=4) or removal/revision of spinal instrumentation along w/ HBOT and antibiotics (n=2): 83% (5/6) Recurrence at f/u ranging from 5 mos – 3 yrs: 0 **Larsson (1992)** Resolution w/ a combination of antibiotics and HBOT: 100% (7/7) ***Cranial osteomyelitis*** **Overall** HBOT may be an effective adjunct to antibiotic to avoid surgery among pts w/ cranial osteomyelitis **Larsson (1992)** Resolution among uncomplicated osteomyelitis w/ no known risk factors: 80% (12/15) Resolution among pts w/ known risk factors: 94% 15/16 **Sandner (2009)** Resolution w/ a combination of antibiotics, surgical debridement and HBOT: 80% (8/10) ***Malignant external otitis osteomyelitis*** **Overall**	

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
				HBOT appears to effective in cases of malignant external otitis osteomyelitis refractory to std tx **Davis (1992)** Resolution w/ a combination of antibiotics and HBOT: 100% (16/16) Recurrence at 4 yrs: 0 **Martel (2000)** Resolution w/ a combination of antibiotics and HBOT w/o surgery: 95% (20/22) **Naronzy (2006)** Resolution: 87.55 (7/8) **Tisch (2006)** Resolution w/ a combination of antibiotics and HBOT: 95% (21/22) **Sternal osteomyelitis** **Overall** HBOT is effective in reducing the need for sterna debridement and/or extensive surgical interventions **Barili (2007)** Relapse: HBOT: 0% Control (antibiotics and surgical debridement only): 33.3% *P*=0.024 Antibiotic duration/ days (SD) HBOT: 47.8 (7.4) Matched controls: 67.6 (25.1) *P*=0.036	

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				Hospital stay/day (SD) HBOT: 52.6 (9.1) Matched controls: 73.6 (24.5) *P*=0.026 **Higuchi (2006)** Complete healing w/o surgery: 50% (2/4)	
Goldman (2009) Systematic review and meta-analysis to evaluate the evidence of the efficacy of HBOT for wound healing and limb salvage **Refractory osteomyelitis** Chen et al. (2004) (n=13) Chen et al. (1998) (n=15) Esterhai et al. (1987) (n=28) Davis et al. (1986) (n=38) Morrey et al. (1979) (n=40)	*Included studies:* 5 *Search dates:* 1978-2008 *Data sources:* Ovid MEDLINE for RCTs, cohort studies and time series and case series *Inclusion criteria:* Human studies, including HBOT and osteomyelitis *Exclusion criteria:* Retrospective uncontrolled trials; <5 participants; central nervous system conditions; late effects of radiation; acute wounds associated w/ multiple trauma and critical care, including necrotizing fasciitis and crush injury *Quality assessment:* Based on GRADE criteria	*Study design* 1 nonrandomized controlled trial, 4 case series w/ time comparison *Total sample size (range)* 149 (13-40) *Age* Range 38-41 *Duration of osteomyelitis (range)* 6 mos – 50 yrs	*HBOT dose (range)* 2.0-2.5 ATA, 90-120 mins, 4-45 sessions *Primary outcomes:* "Cure," recurrence	*"Cure" (% pts)* Esterhai et al. (1987): HBO grp, 79% (11/14); control grp 93% (13/14), *P*=0.28 Davis et al. (1986): 89% Morrey et al. (1979): 85% Chen et al. (2004): 92% Chen et al. (1998): 87% *Recurrences (# pts):* Davis et al. (1986): 0 Morrey et al. (1979): 6 Chen et al. (1998): 0 Chen et al. (2004): 0 Esterhai et al. (1987): HBOT grp 2, non-HBOT grp 1 *Eradication of osteomyelitis (%)* Esterhai et al. (1987): HBOT grp: 79% Non-HBOT grp: 93%	*Author's conclusions* Conflicting data. 4 poor-quality case series (rated moderate by author) found HBOT to be an effective adjunct to std tx for osteomyelitis, 1 poor-quality nonrandomized controlled trial reported lower % cure rate among pts receiving HBOT than controls. *Limitations* Individual study quality was rated moderate in a number of cases when it should have been low. *Quality of review* Fair

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Lawson (2003) STEER by the Wessex Institute for Health Research and Development (UK) to review the effects of HBOT tx in people w/ osteomyelitis Esterhai et al. (1987) (n=28)	*Included studies:* 1 (2 systematic reviews w/ both including the same nonrandomized controlled trial, 3 small case series identified but not discussed) *Search date:* August 2003 *Data sources:* MEDLINE; Embase; Cochrane Library; British Medical Journal Publishing Group Clinical Evidence; NHS Centre for Reviews and Dissemination, NHS Economic Evaluation Database; ISI Science Citation Index; manually searched identified reviews for further references. *Inclusion criteria:* People of any age w/ osteomyelitis; HBOT alone or as an adjunct to other txs; systematic reviews w/ clear questions, listed database searched, stated inclusion and exclusion criteria; all controlled trials providing results for	Esterhai et al. (1987) Study design nonrandomized controlled trial *Sample size* 28 *# HBOT sessions* NR *Comparators* Surgical debridement plus intravenous antibiotics *F/u* 41.1 mos *Risk of bias (# studies)* High risk of bias	Esterhai et al. (1987) *HBOT dose* 2 ATA for 120 mins per day, 6 days per wk *Outcomes* Symptoms, signs, functional outcomes, disability, clinical complications of osteomyelitis *Harms* Any AE	*Outcomes* **Esterhai et al. (1987):** Success rate: HBOT grp 79% (11/14); control grp 93% (13/14), *P*=0.28 Infection recurrence: HBOT grp 14% (2/14); control grp 7% (1/14), *P*=0.54 Duration of hospital stay: Mean stay HBOT grp 54 days vs 47 days control (NS) *Harms* Transient myopia, barotraumatic otitis, seizures secondary to O_2 toxicity (including 1 death); pneumothorax and pulmonary edema (including 1 death)	*Author's conclusions* There is insufficient evidence regarding the safety and efficacy of HBOT, w/ or w/o other tx, for the tx of people w/ osteomyelitis. *Limitations* This was a rapid review so unpublished high quality data may have been omitted; the 1 included study had a high risk of bias and likely inadequate power to detect a significant difference between grps. *Quality of review* Fair

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	people w/ osteomyelitis separately from those w/ other conditions *Exclusion criteria:* Case series w/ <30 participants; studies where osteomyelitis was not stated as an inclusion criteria or which did not stratify results by condition *Comparator:* Any tx regimen that does not involve HBOT *Quality assessment tool:* Described narratively				
LRTI					
Bennett et al. (2012) Cochrane Collaboration A systematic review to assess the benefits and harms of HBOT for treating or preventing LRTI Annane et al. (2004) (n=68)	*Included studies:* 11 *Search dates:* Up to March 2012 *Data sources:* Cochrane library, MEDLINE, Embase, EBSCO CINAHL (1982-2008); DORCTIHM (database of randomized trials in hyperbaric medicine) to 2008, manually searched	*Study design* 11 RCTs *Sample size* 669 (range 7-160) *# HBOT sessions* 30 sessions in all but 1 study where pts received 40 sessions *F/u* Immediately posttx	*HBOT dose (range)* 2.0-3.0 ATA for 80-90 mins *Primary outcomes* Death; complete resolution of necrosis or tissue damage; complete resolution or improvement of necrosis or tissue damage; achievement of complete mucosal cover; establishment of bony	<u>All anatomical areas</u> *Complete resolution of tissue damage or necrosis ≤3 mos* Overall: 4 trials (n=325) HBOT grp 36%, control 28% (I^2=82%) Resolution for pts requiring hemimandibulecotomy Marx (1999a): RR 1.4; 95% CI 1.1-1.8 *P*=0.001 Resolution for pts w/ radiation proctitis Clarke (2008): RR 9.7; 95% CI 0.6-170.1, *P*=0.12) Resolution for pts w/ ORN of the mandible Annane (2004): RR 0.6; 95% CI 0.25-1.4, *P*=0.24,	*Author's conclusions* There is some evidence that HBOT tx improves outcomes in LRTI affecting bone and soft tissues of the head and neck, for radiation proctitis and to prevent the development of ORN following tooth extraction in an irradiated field; there was no evidence of an

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Clarke et al. (2008) (n=150) Gothard et al. (2010) (n=58) Hulshof et al. (2002) (n=7) Marx et al. (1985) (n=74) Marx (1999a) (n=104) Marx (1999b) (n=160) Pritchard et al. (2001) (n=34) Schoen et al. (2007) (n=26) Sidik et al. (2007) (n=65) Teguh et al. (2009) (n=19)	bibliographies for additional eligible trials; unpublished data sought *Inclusion criteria:* RCTs and pseudo-RCTs that compared the effect of a regimen, including HBOT, on any form of LRTI, w/ any tx regimen not including HBOT; any person w/ LRTI (including necrosis) of any tissue; any pt having received large-dose radiotherapy likely to induce relatively early necrosis (e.g., radiosurgery to brain); HBOT doses from 1.5-4.0 ATA for 30-120 mins *Exclusion criteria:* Trivial txs on the hand Eligible comparators: Any standard tx regimen designed to promote tissue healing or prevent further deterioration *Quality assessment:* Based on Cochrane risk of bias criteria	to 1 yr *Risk of bias (# studies)* Varied widely across studies Overall risk of bias (judged from the individual domains provided): Unclear or high: 6 Medium: 2 Low: 2 Anatomical areas (# studies) H&N: 5 Arm/shoulder: 2 Rectum: 1 Cervix; 1 Unspecified: 1 Radiation exposure: Varied widely w/ most studies not specifying a minimum dose	continuity; improvement in LENT-SOMA; wound dehiscence; loss of dental implant *Secondary outcomes* Resolution of pain; resolution of swelling; improvement in QOL, function or both; improvement in x-ray appearance *Harms* Death; recurrence of tumor; visual disturbance; barotrauma; oxygen toxicity; w/drawal from tx; any other reported adverse event	*Complete resolution or significant improvement of tissue damage or necrosis* Clarke (2008): HBOT grp 46%, control 27% (RR 1.72; 95% CI 1.0-2.9, *P*=0.04) *LENT-SOMA scores (mean improvement)* Clarke (2008): HBOT 5, control 2.6; (MD 2.4; 95% CI 0.89-3.9, *P*=.002) *QOL/Functional outcomes* SF-36 for general health at 12 mos Pritchard (2001): Mean score HBOT grp 58.8, control 61.1 (WMD –2.3; 95% CI –19.0-14.4, *P*=0.79) *SF-36 for physical functioning at 12 mos* Pritchard (2001): Mean score HBOT grp 53.5, control 57.5 (WMD –4.0; 95% CI –19.4-11.4, *P*=0.61) *Bowel bother subscale* Clarke (2008) pre-post mean improvement: HBOT grp 14.1% (*P*=0.0007); control grp 5.8% (*P*=0.15) *Lymphedema-specific functioning effect at 12 mos* Gothard (2010): Median score (1-100) HBOT grp 37.5 (IQR 20.8-52.1), control grp 45.8 (13.0-62.5) (NS) *QOL in H&N cancers at 12 mos* Teguh (2009): H&N 35 sticky saliva score (0=nil,100=max) HBOT grp 25, control 62 (*P*=0.01); H&N 35 scores for dry mouth (same scale) HBOT grp 28, controls 92 (*P*=0.009); H&N 35 scores for difficulty swallowing (same scale) HBOT grp 7, controls 40 (*P*=0.011); VAS for dry mouth (0=nil,	effect on neurological tissue and no benefit. *Limitations* Individual studies varied in the amount of radiation exposure prior to HBOT tx; inclusion criteria varied among studies; meta analysis was unsuitable for most outcomes due to significant heterogeneity between studies. *Quality of review* Good

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				10=max) HBOT grp 3.4, controls 7.2 (*P*=NR); VAS for pain in the mouth (same scale) HBOT grp 0.8, controls 6.6 (*P*<0.0001) *QOL following dental implants in irradiated area* Schoen (2007): Global QOL (0-100 scale), HBOT grp 66.7±13.6, controls 84.3±19.7 (MD 17.6 points; 95% CI 2.8-32.2, *P*=0.02) (results unreliable due to differences in baseline scores between grps) <u>*ORN*</u> *Achievement of complete mucosal cover* 3 trials (n=246) HBOT grp 84%, controls 65% (I^2=27%) (RR 1.3; 95% CI 1.1-1.6, *P*=0.003) *Establishment of bony continuity* Marx (1999a): HBOT grp 92%, controls 65% (RR 1.5; 95% CI 1.1-1.8, *P*=0.001) *Healing of tooth sockets following extraction in irradiated field at 6 mos* Marx (1985): HBOT grp 95%, controls 26% (RR 1.4; 95% CI 1.1-1.7, *P*=0.009) <u>*H&N tissues*</u> *Wound dehiscence* 2 trials (n=368), HBOT grp 6%, control 28% (RR 4.2; 95% CI 1.1-16.8, *P*=0.04) (I^2=70%) *Loss of dental implant* Schoen (2007): Risk of losing an implant was 2.5 greater in the HBOT compared w/ control (RR 2.5; 95% CI 0.59-10.64, *P*=0.22) <u>*Harms*</u>	

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
				Overall adverse events Ear pain 16% (Clarke 2008) Transient myopia 3% (Clarke 2008); 8% (Gothard 2010) Confinement anxiety 1.7% (Clarke 2008) Well tolerated (Schoen 2007, Teguh 2009) *Death* Annane (2004): RR of dying following HBOT tx 0.84 (95% CI 0.13-5.61)	
Fritz et al. (2010) Virginia Commonwealth University A systematic review to evaluate the use of HBOT in preventing ORN after tooth removal in irradiated pts Ben-David et al. (2007) (n=176) Sulaiman et al. (2003) (n=187) Chavez and Adkinson (2001) (n=40) David et al. (2001) (n=24) Vudiniabola et al. (1999) (n=37) Marx et al. (1985) (n=74)	*Included studies:* 7 (an additional 7 studies were included in this review but did not use HBOT tx) *Search dates*: January 1948 – March 2008; MEDLINE database *Inclusion criteria:* RCTs, nonrandomized controlled trials, case control studies, retrospective studies and case series; pts had to have received a radiation dose ≥60 Gy; had to state # subjects and teeth w/ ORN *Exclusion criteria:* Non-English language; HBOT for existing ORN; animal studies	*Study design* 1 RCT, 6 observational studies *Sample size* 585 (range 24-188) *# HBOT sessions* 30 sessions (3 studies did not report # sessions) *Comparators* Marx (1985) compared HBOT tx w/ antibiotics *F/u* NR *Risk of bias (# studies)* Overall, high to unclear risk of bias among included	*HBOT dose (range)* 2.4 ATA for 90 mins (3 studies did not report dose) *Primary outcome* ORN	*Incidence of ORN* Marx (1985) HBOT grp: 5.4% Control grp: 29.9: *P*=0.005 Ben-David (2007): 0% Sulaiman (2003): 0% Chavez and Atkinson (2001): 11% David (2001): 4.2% Vudiniabola (1999): 4% Beumer (1983): 0%	*Author's conclusions* Insufficient evidence to determine if HBOT tx reduces the incidence of ORN in irradiated pts requiring tooth extraction. *Limitations* Poor reporting, small sample sizes, high risk of selection bias, detection bias and performance bias. *Quality of review* Fair

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Beumer et al. (1983) (n=72)	*Quality assessment:* 5 criteria used for assessment of RCTs (randomization, allocation concealment, blinding, completeness of f/u, ITT); 3 criteria used for assessment of observational studies (was the population adequately defined, inclusion/exclusion criteria, completeness of f/u)	studies Radiation exposure: All but 1 study reported >50 Gy; 1 study did not report radiation exposure ORN definition: 2 studies described ORN as exposed irradiated bone present for 3-6 mos; 1 study used a common terminology criteria for adverse events as a definition, 1 study defined ORN as nonviable irradiated bone, which fails to heal w/o intervention, 3 studies did not state a definition			
Nabil and Samman (2011) University of Hong Kong A systematic review evaluating the incidence and factors influencing the development of ORN after tooth	*Included studies:* 19 total w/ just 8 studies reporting use of HBOT tx *Search dates:* 1950 – April 2010 *Data sources:* MEDLINE, Embase, Cochrane library *Inclusion criteria*: All studies reporting ORN	*Study design of HBOT studies* 1 RCT; 1 prospective cohort, 6 retrospective cohorts *Sample size (reflecting only those pts undergoing HBOT tx and their comparators)* 433 (range 13-107)	*HBOT dose* 2.4 ATA for 90 mins *Primary outcome* Occurrence of ORN at the extraction socket *Harms* Not specified a priori	*ORN incidence (including both HBOT tx'd pts and non-HBOT tx'd pts, 19 studies):* 7% *ORN incidence among HBOT tx'd pts* *Total ORN incidence*: 4% *ORN incidence per tooth:* 2% Marx (1985): HBOT 5.4%; controls 29.9% (*P*=0.005) <u>*Subgrp analysis*</u> 0 cases (following post-irradiation extraction) of ORN among 29 pts receiving a radiation dose <60	*Author's conclusions* HBOT appears effective in preventing ORN in pts needing extraction; In the absence of contraindications, pts having received a radiation dose >60 Gy for the tx of head and neck cancer and requiring extraction of mandibular teeth w/in the radiated

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extraction in irradiated H&N cancer pts **Studies using HBOT** Koga et al. (2008) (n=57) Ben-David et al. (2007) (n=176) Sulaiman et al. (2003) (n=187) Chavez and Adkinson (2001) (n=40) David et al. (2001) (n=24) Lambert et al. (1997) (n=46) Marx et al. (1985) (n=74) Beumer et al. (1983) (n=72)	occurrence following tooth extraction in irradiated H&N cancer pts; ≥5 pts; consecutive enrollment; mandible and/or maxilla must have been affected; dx of ORN made after clinical exam; ORN occurred at site of extraction; ≥3-mo f/u for individual pts; ≥6 mo f/u for grps of pts *Exclusion criteria:* Pts w/ irradiation of the H&N region that did not include the maxilla or mandible; ORN present before tooth extraction *Quality assessment tool:* NR	*# HBOT sessions* 30 *Comparators* Antibiotics *Risk of bias* NR *F/u (range)* 2.5-42.8 mos *# teeth extracted among pts receiving HBOT* 595 *Radiation exposure* NR in review *ORN definition* Area of exposed devitalized irradiated bone that failed to heal over 3 mos w/ no evidence of recurrence of neoplastic disease		Gy, but 28 cases (12%) among pts receiving a radiation dose >60Gy following post-irradiation extraction	field are at the highest risk of developing ORN and may benefit most from HBOT. *Limitations* Poor-quality studies w/ likely high risk of bias; no formal assessment of study quality; poor reporting of individual study data. *Quality of review* Fair
Brain Injury					

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Bennett et al. (2009) Cochrane Collaboration A systematic review to assess the benefits and harms of adjunctive HBOT for acute TBI Artru et al. (1976a) (n=60) Holbach et al. (1974) (n=99) Ren et al. (2001) (n=55) Rockswold et al. (1992) (n=168) Xie et al. (2007) (n=60)	*Included studies*: 5 *Search dates*: Up to January 2009 *Data sources*: CENTRAL, MEDLINE, Embase, CINAHL, DORCTIHM), manually searched bibliographies for additional eligible trials; unpublished data sought *Inclusion criteria:* RCTs and quasi-RCTs comparing the effect of tx for acute TBI w/ HBOT as an adjunct tx w/ similar txs w/o HBOT; persons admitted to an intensive care or intensive neurosurgical facility w/ an acute TBI following blunt trauma; HBOT dose between 1.5-3.5 ATA for 30-120 mins at least once *Exclusion criteria:* Comparator interventions undertaken in a nonspecialized acute care setting *Eligible comparators:* Any standard tx regimen designed to maximize	*Study design* 5 RCTs *Sample size* 442 *# HBOT sessions* Range 10.5-40 *F/u* Immediately posttx to 1 yr *Risk of bias* Overall risk of bias (judged from the individual domains provided): Unclear or high: 4 Medium: 1 *Type of head injury* All 5 studies included pts w/ severe closed head injury *Severity of injury* Artru (1976a): Jouvet scale, (grp mean 9.39 vs 9.59, NS) Holbach (1974): Comatose on admission Ren (2001): GCS <9 Rockswold (1992):	*HBOT dose (range)* 1.5-2.5 ATA for 40-60 mins *Primary outcomes* Functional outcome; mortality *Secondary outcomes* Intracranial pressure; progress of GCS *Harms* Adverse events of HBOT	*Proportion of pts w/ unfavorable functional outcome at end of tx-4 wks* Two studies (Artru 1976a; Holbach 1974, n=159) RR of a poor outcome w/ HBOT: 0.38, 95% CI 0.10-1.37, *P*=0.14) (I^2=72%) Absolute risk difference: 22.4% (*P*=0.04); NNT to achieve one extra good outcome: 4 (95% CI 3-11). *Proportion of pts w/ an unfavorable functional outcome at 6 mos* One study (Ren 2001, n=55), RR unfavorable outcome w/ HBOT: 0.36, 95% CI 0.18-0.72, *P*=0.004; absolute risk difference: 22.3%, *P*=0.04; NNT for one extra good outcome: 4 (95% CI 3-11) *Proportion of pts w/ an unfavorable functional outcome at 1 yr* One study (Rockswold 1992, n=168) RR: 1.02, 95% CI 0.77-1.36, *P*=0.87 *Proportion of pts w/an unfavorable outcome at final assessment (any time)* 4 studies (Holbach 1974, Ren 2001, Artru 1976, Rockswold 1992, n=382) RR for unfavorable outcome w/ HBOT: 0.51, 95% CI 0.25-1.08, *P*=0.08). (I^2=81%) Best case scenario: Absolute risk difference: 18% (sig but *P* value NR) NNT to avoid one poor outcome: 6, 95% CI 4-12. *Mortality reported at any time* 4 studies (Holbach 1974, Artru 1976a, Rockswold 1992, Xie 2007, n=387) RR of dying if given HBOT: 0.69, 95% CI 0.54-0.88,	*Author's conclusions* Limited evidence suggests an improvement in survival w/ the addition of HBOT following severe brain injury; but little to suggest that HBOT improves functional outcomes or ability to perform activities of daily living. *Limitations* Small # trials available w/ small overall sample size; high risk of bias among included trials; several planned subgrp analysis were not possible; no std severity index was employed across trials; HBOT protocol varied across studies; comparator txs were poorly described; incidence of harms were poorly assessed overall. *Quality of review* Good

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	brain protection and promote recovery from TBI *Subgrp analysis:* Considered where appropriate for age, dose, nature of comparators, severity of injury, nature of injury *Quality assessment:* Based on Cochrane risk of bias criteria	GCS <10 Xie (2007): GCS 3-12 *Time between injury and enrollment:* Reported in 1 study (Xie (2007): 24 hrs *F/u* Artru (1976a): 1 yr Holbach (1974): Immediately following tx Ren (2001): 6 mos Rockswold (1992): 1.5 yrs Xie (2007): Immediately following tx		*P*=0.003, (I^2=0%) Absolute risk difference: 15% NNT to avoid 1 death by applying HBOT: 7, 95% CI 4-22. *Progress of GCS* 1 study (Xie 2007, n=60) Improved GCS among HBOT grp compared w/ controls (MD 3.6 pts, 95% CI 2.5-4.7, *P*<0.00001) *Subgrp analysis* Tx pressure Unfavorable functional outcome at 2.5 ATA: RR 0.48, 95% CI 0.27-0.87, *P*=0.01 Unfavorable outcome at 1.5 ATA: RR 0.47, 95% CI 0.08-2.85, *P*=0.41 (I^2=89%) HBOT w/ myringotomy HBOT w/ myringotomy: Intracranial pressure (MD, –8.2 mm Hg, 95% CI –14.7 mm Hg to –1.7 mm Hg, *P*=0.01 HBOT w/o myringotomy: Intracranial pressure (MD, 2.7 mm Hg, 95% CI –5.9 mm Hg to 11.3 mm Hg, *P*=0.54 *Harms* Pulmonary effects of HBOT 2 studies (Artru 1976a, Rockswold 1992, n=228) 15 pts (13% of total receiving HBOT had severe pulmonary complications compared w/ none in control grp RR 15.57, 95% CI 2.11-114.72, *P*=0.007 (I^2=0%) NNT for 1 adverse effect=8, 95% CI 5-15 Neurological oxygen toxicity 1 study (Rockswold 1992, n=168), 2 pts (2.3%) receiving HBOT had isolated generalized seizures	

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				compared w/ none in control grp RR 5.0, 95% CI 0.24-102.6, *P*=0.3 Middle ear barotrauma One study (Rockswold 1992, n=168), 2 pts (2.3%) receiving HBOT had a hemotympanum compared w/ none in control grp, RR 5.0, 95% CI 0.24-102.6, *P*=0.3	
McDonagh et al. (2003) AHRQ A systematic review to assess the benefits and harms of HBOT for brain injury, CP, and stroke TBI Artru et al. (1976a) (n=60) Artru et al. (1976b) (n=6) Hayakawa et al. (1971) (n=13) Mogami et al. (1969) (n=66, 55 w/ TBI) Ren et al. (2001) (n=55) Rockswold et al. (1985, 1992, 1994) (n=168) Rockswold et al. (2001) (n=37)	*Included studies:* 13 TBI 8, other brain Injury 4 *Search dates*: Inception to July 2003 *Data sources*: MEDLINE, PreMEDLINE, Embase, CINAHL, Cochrane Library, Health Technology Assessment Database, HealthSTAR, AltHealth Watch, MANTIS), manually searched bibliographies for additional eligible trials; unpublished data sought *Inclusion criteria*: Any tx using 100% oxygen inside an HBO chamber >1 ATA, any frequency, any duration, any # sessions; pts w/ brain injury from any cause and at any stage; human subject studies w/ original data;	*Study design* TBI: Controlled trials 2, observational studies 6 Other brain Injury: Controlled trials 1, observational studies 3 *Sample size* Range, 6-336 *# HBOT sessions (range)* Varied among studies Artru (1976a): Daily for 12 days Rockswold (1985, 1992, 1994): Every 8 hrs for 2 wks or until pt regained consciousness (mean 21) Rockswold (2001): Mean 5	*HBOT dose (range)* 1.5-2.5 ATA for 60 mins *Outcomes* Mortality; consciousness; independence in daily living; duration of coma *Harms* CNS toxicity; pulmonary complications; ear problems	**TBI** Trials (2 controlled trials Artru, 1976a; Rockswold 1985, 1992, 1994) *Mortality* Artru 1976a: No effect at 12 mos (HBOT grp 15/31 [48%], control 16/29 [55%], *P*=NS) Rockswold 1985, 1992, 1994: Significant decrease at 12 mos (HBOT grp 14/84 [17%], control 26/84 [31%, *P*=NR) *Consciousness at 1 mo* Artru 1976a: HBOT grp 13/31 (42%), controls 8/29 (28%), *P*=NS *Independent in daily living at 1 yr* Artru 1976a: HBOT grp 14/31 (45%), controls 12/29 (41%), *P*=NS *Mean duration of coma* Artru 1976a: HBOT grp 28.2 day, controls 32.7 days, *P*=NS *Dead or severely disabled at 1 yr* Rockswold (1985, 1992, 1994): HBOT grp 40/84 (48%), control 40/84 (48%) (*P*=NS) Observational studies (2 medium risk of bias, Artru	*Author's conclusions* Insufficient evidence to determine the benefits and harms of HBOT for the tx of TBI and other brain injuries. *Limitations* Difficult to compare studies because of the use of different scales, differences between pts at baseline, different tx protocols; poor internal validity in many studies. *Quality of review* Good

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Sukoff et al. (1982) (n=50) Other brain injuries Chuba et al. (1997) (n=10) Imai et al. (1974) (n=32) Jianhua et al. (1995) (n=92) Mathieu et al. (1987) (n=136) Shn-rong (1995) (n=336)	before-after or time-series w/ >5 cases and outcomes reported for before and after tx *Exclusion criteria:* Case reports; use of HBOT for approved indications such as carbon monoxide poisoning or acute air embolism; studies reporting only intermediate outcomes *Quality assessment:* Based on AHRQ methods modified to address issues particular to HBOT; rating according to USPSTF methods	*Duration between injury and beginning tx:* Artru (1976a): Mean 4.5 days Rockswold (1985, 1992, 1994): Typically w/in 24 hrs Rockswold (2001): Mean 23 hrs (SD 2) *Risk of bias* Artru (1976a): Medium Artru (1976b): High Hayakawa (1971): High Ren (2001): High Rockswold (1985, 1992, 1994): Medium Rockswold (2001): Medium Sukoff (1982): High Other brain injuries Chuba (1997): High Imai (1974): High Jianhua (1995): High Mathieu (1987): High		1976b, Rockswold 2001) Artru 1976b: 3 of 6 pts died, 1 did not recover consciousness, 2 recovered consciousness but had severe morbidity; no relationship between outcomes and pre- or post-HBOT cerebral blood flow or metabolism Mogami (1969); Hayakawa (1971); Sukoff (1982); Rockswold (2001): No outcomes of interest **Other brain injuries** Jianhua (1995): Significantly higher proportion of pts cured in HBOT grp vs controls: 38% (18/47) vs 18% (8/45), *P*<0.05 Mathieu (1987): 7% mortality among pts following HBOT Imai (1974): 5%-10% improvement in memory (Bender-Gestalt memory test and 7 unvalidated measures were used to create a memory score) Chuba (1997): 40% (4/10) improvement in symptoms among children w/ radiation induced necrosis of the central nervous system Shn-rong (1995): Cure rate of 68% (65/95) following HBOT among pts in a coma for a variety of etiologies ***Subgrp analysis*** Regaining consciousness: Artru (1976a): Younger pts (age <30 yrs) were more likely to recover consciousness by I mo following HBOT compared w/ controls (6/9 vs 1/9, *P*<0.03) HBOT w/ myringotomy: Rockswold 1985, 1992, 1994) (see Bennett 2009)	

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				Harms CNS toxicity: Rockswold (1985, 1992, 1994) reported seizures in 12% of HBOT tx'd pts; no reported seizures in CP trials Pulmonary complications: Artru (1976a): Tx was stopped in 35% of sessions (11/31) due to pulmonary sx Rockswold (1985, 1992, 1994): Tx was permanently stopped in 12% of cases(10/84) due to pulmonary sx	
Cerebral Palsy					
McDonagh et al. (2007) Paper publication of a 2003 AHRQ report (updated) A systematic review to assess the benefits and harms of HBOT for CP Chavdarov (2002) (n=50) Collet et al. (2001) (n=111) Machado (1989) (n=230) Montgomery et al. (1999) (n=25) Packard (2000)	*Included studies*: 6 *Search dates:* Inception to June 2005 *Data sources:* MEDLINE, Embase, CINAHL, Cochrane library, HealthSTAR, AltHealth Watch, MANTIS, DARE, bibliographic database from the Undersea and Hyperbaric Medical Society; Database of RCTs in Hyperbaric Medicine; the libraries of the European Underwater and Baromedical Society; International Congress of Hyperbaric Medicine; National Baromedical	*Study design* 2 RCTs, 4 observational studies *Sample size* Range 6-230 *# HBOT sessions (range)* Varied among studies Collet (2001): 40 sessions Montgomery (1999): 20 Rockswold (2001): Mean 5 *Risk of bias* Chavdarov (2002): Medium (our	*HBOT dose* Collet (2001): 1.75 ATA for 60 mins Montgomery (1999): Employed different protocols across centers *Outcomes* Disease-specific motor function; caregiver assessment *Harms* No a priori assessment of adverse events but adverse events were reported	**Motor function** *Collet (2001)* (mean change in GMFM scale among children immediately posttx): HBOT grp 2.9, control 3.0, *P*=NS *Collet (2001)* (mean change in GMFM scale among children 6 mos posttx): HBOT grp 3.4, control 3.1, *P*=NS *Montgomery (1999)* (mean change in GMFM scale posttx: 5.3% improvement among pts receiving HBOT *Chavdarov (2002):* Reported improvements of 13% for motor, 6% for cognitive, and 7% for speech abilities 2 days post HBOT *Waalkes (2002):* Mean GMFM scores improved at each time period *P*<0.05 (data NR)	*Author's conclusions* Insufficient evidence to determine the benefits and harms of HBOT for CP. *Limitations* Comparisons across studies was difficult due to baseline differences and different HBOT protocols; Chavdarov (2002) was described as high risk of bias in the original 2003 report and considered high risk of bias by our assessment. *Quality of review* Good

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(n=26) Waalkes et al. (2002) (n=7)	Services Inc.), manually searched bibliographies for additional eligible trials; searched the Textbook of Hyperbaric Medicine; unpublished data sought *Inclusion criteria:* English language; original data from pts w/ CP; any HBOT protocol; functional outcomes evaluated *Exclusion criteria*: Case reports and case series; animal studies; intermediate outcomes *Quality assessment :* Based on checklists from the USPSTF and the National Health Services Center for reviews and dissemination, modified to address issues specific to HBOT	assessment and 2003 McDonagh assessment was high risk of bias) Collet (2001): Medium Machado (1989): High Montgomery (1999): Medium Packard (2000): High Waalkes (2002): Medium		**Caregiver viewpoint (PEDI scale)** *Collet (2001):* Control grp had sig better mobility and social functioning (data NR) *Packard (2000):* Reported no difference between grps in PEDI scores according to results from blinded assessors (results NR) but found a significant improvement in PEDI mobility subscore favoring HBOT among unblinded parents **Other disease-specific outcomes** *Machado (1989):* Reported 95% reduced spasticity immediately post HBOT, which persisted among 76% of 82 children at 6 mos f/u **Harms** Ear problems: Collet (2001) reported ear problems among 47% of children receiving HBOT and 22% among controls (*P* sig but value NR; Packard (2000) reported 35% pts reported ear problems related to pressure; Montgomery (1999) reported 52% children required tympanostomy tube placement Seizures: Packard (2000) reported 12% seizure rate among children; Chavdarov (2002) reported 8% of children stopped tx due to adverse events, including seizures; Machado (1989) reported 1 seizure	
Multiple Sclerosis					
Bennett and Heard (2011) Cochrane Collaboration	*Included studies:* 10 reports of 9 trials *Search dates:* Up to May 2011	*Study design* 9 RCTs (10 publications) Sample size 504 (range 17-120)	*HBOT dose (range)* 1.75-2.5 ATA for 90 mins *Primary outcomes* Grp mean differences in	*Primary outcomes* *Improvement in mean EDSS at end of tx (20 sessions):* 5 trials (n=271) contributed to this outcome (Fischer 1983, Neiman 1985, Harpur 1986, Wiles	*Author's conclusions* No consistent evidence to confirm a tx benefit of HBOT for MS, 2 studies reported generally

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An update of a 2004 systematic review to assess the benefits and harms of HBOT for treating MS Barnes et al. (1985) (n=120) Barnes et al. (1987) (n=120) Confavreux et al. (1986) (n=17) Fischer et al. (1983) (n=40) Harpur et al. (1986) (n=82) L'Hermitte et al. (1986) (n=49) Neiman et al. (1985) (n=24) Oriani et al. (1990b) (n=44) Wiles et al. (1986) (n=84) Wood et al. (1985) (n=44)	*Data sources:* Cochrane MS Group's Specialized Register, CENTRAL, MEDLINE, Embase, CINAHL LILACS, PEDro, clinical trials registries, manually searched bibliographies for additional eligible trials; unpublished data sought *Inclusion criteria:* RCTs of HBOT vs placebo or no tx; all MS pts regardless of stage of disease *Quality assessment:* Based on Jadad score	*# HBOT sessions* 20 sessions over 4 wks *Comparators* 4 studies used air administered at a trivial pressure (PIO_2 ~16 7 mm Hg and PIN_2 ~608 mm Hg) 4 studies used nitrogen-enriched air to achieve a PIO_2 152 mm Hg, PIN_2 1100-1345 mm Hg; 1 study used air at the same pressure as the tx grp *F/u* Immediately posttx to 1 yr *Risk of bias (# studies)* W/ exception of allocation concealment (which was unclear in many trials); included studies generally had a low risk of bias	EDSS pretx to immediately posttx, 6 mos posttx and 1 yr posttx; improvement defined as a decrease of ≥1 point on EDSS at end of tx, 6 mos and 1 yr; Exacerbation of the disease *Secondary outcomes* Functional scores assessed by neurologist and those pt reported (e.g., Kurtzke FSS at completion of intervention, 6 mos or 1 yr; # pts w/ a change in individual elements of FSS; subjective ratings on improvement in individual elements of the FSS *Harms* # pts suffering side effects or AE associated w/ tx (specifically aural barotrauma and visual disturbances), including those who dropped out	1986, Oriani 1990b); no sig reduction in the mean EDSS in HBOT grp vs sham (mean change in HBOT grp vs sham, –0.07, 95% CI –0.23-0.09, *P*=0.4 (Chi2=9.48, *P*=0.05) *Improvement in mean EDSS 6 mos posttx:* 3 trials (n=163) contributed to this outcome (Fischer 1983, Harpur 1986, Oriani 1990b); no sig reduction in the mean EDSS in HBOT grp vs sham (mean change in HBOT grp vs sham, –0.22, 95% CI –0.54-0.09, *P*=0.17 (Chi2=7.55, df=2, *P*=0.023) *Improvement in mean EDSS 1 yr posttx:* 2 trials (n=81) contributed to this outcome (Fischer 1983, Oriani 1990b); a sig reduction in the mean EDSS in HBOT grp vs sham (mean change in HBOT grp vs sham, –0.85, 95% CI –1.28 to –0.42, *P*=0.0001 (no sig heterogeneity) *# pts not improved by at least 1 point on EDSS at end of tx:* 8 trials (n=411) contributed to this outcome (Barnes 1985, Barnes 1987, Confavreux 1986, Fischer 1983, Neiman 1985, Harpur 1986, L'Hermitte 1986, Oriani 1990b, Wood 1985); in 3 trials no pts were improved in either arm; a meta-analysis of the remaining 5 trials found a 5% (n=11) improvement among HBOT tx'd pts and 1.5% (n=3) improvement among sham pts (odds of no improvement, OR 0.33, 95% CI 0.09-1.18, *P*=0.09) (no sig heterogeneity) *# pts not improved by at least 1 point on EDSS at 6 mos posttx:* 7 trials (n=363) contributed to this outcome	positive findings while the remaining 7 reported no evidence of a tx effect. Evidence does not justify routine use; modest tx benefits may be present for those w/ mild disease but further study of HBOT for MS is not justified by this review. *Limitations* Small sample size overall; trials were dated and sometimes difficult to interpret. *Quality of review* Good

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				(Barnes 1985, Barnes 1987, Confavreux 1986, Fischer 1983, Neiman 1985, Harpur 1986, L'Hermitte 1986, Oriani 1990b); in 3 trials no pts were improved in either arm; a meta-analysis of the remaining 4 trials found an 8.3% (n=16) improvement among HBOT tx'd pts and 4.7% (n=8) improvement among sham pts (odds of no improvement, OR 0.42, 95% CI 0.16-1.08, *P*=0.07) (no sig heterogeneity) *# pts not improved by at least 1 point on EDSS at 1 yr posttx:* 3 trials (n=176) contributed to this outcome (Barnes 1985, Barnes 1987, Confavreux 1986, Oriani 1990b); in 1 trial no pts were improved in either arm; a meta-analysis of the remaining 2 trials found a 14.3% (n=13) improvement among HBOT tx'd pts and 4.5% (n=4) improvement among sham pts (odds of no improvement, OR 0.2, 95% CI 0.06-1.08, *P*=0.01, NNT=10, 95% CI 5-7) (no sig heterogeneity) *Prevention of exacerbation during 1 mo of tx:* 1 trial (n=117) contributed to this outcome (Barnes 1985); 1 pt in the sham grp and none in the HBOT grp experienced an exacerbation (odds of exacerbation, OR 0.31, 95% CI 0.01-7.8, *P*=0.5) *Prevention of exacerbation w/in 6 mos:* 2 trials (n=122) contributed to this outcome (Harpur 1986, L'Hermitte 1986); 7 (14.3%) pts in the sham grp and 10 (13.7%) in the HBOT grp experienced an exacerbation (odds of exacerbation, OR 0.74, 95% CI 0.25-2.22, *P*=0.6)	

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
				Prevention of exacerbation w/in 1 yr: 2 trials (n=153) contributed to this outcome (Fischer 1983, Barnes 1987) 28 pts (36.9%) in the sham grp and 20 pts (25.9%) in the HBOT grp experienced an exacerbation (odds of exacerbation, OR 0.38, 95% CI 0.04-3.22, *P*=0.4) <u>*Secondary outcomes*</u> *Global FSS:* 4 trials (Neiman 1985, Harpur 1986, L'Hermitte 1986, Oriani 1990b) (194 participants) were pooled and found 29% improvement in global FSS following 20 txs in the HBOT grp vs 28% in the sham grp (OR, 1.17; 95% CI 0.59-2.33) *Individual FSS* elements: No sig difference between HBOT grps and sham grps in all but 2 trials; 2 trials (Barnes 1987, Oriani 1990b) found that 10 pts (11%) had improved pyramidal function 6 mos posttx in the HBOT grp vs 2 (2.3%) in the sham grp (odds of failing to improve, OR 0.17, 95% CI 0.07-0.78, *P*=0.02, NNT=11, 95% CI 6-63). Oriani (1990b) found that 12 pts (13.2%) had improved pyramidal function 12 mos posttx in the HBOT grp vs 4 (4.5%) in the sham grp (odds of failing to improve, OR 0.13, 95% CI 0.03-0.58, *P*=0.007, NNT=11, 95% CI 6-197). <u>*Subgrp analysis*</u> *Improvement in mean EDSS 6 mos posttx by length of tx:* Fisher (1983) found that there was a sig benefit of HBOT for those having a shorter course of tx (20 sessions vs 20 sessions plus 5 mos of boosters) (shorter course mean change in HBOT grp vs sham, –0.84, 95% CI –1.43 to –0.25, *P*=0.006; longer	

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
				course mean change in HBOT grp vs sham, –0.29, 95% CI –0.91-0.33, *P*=0.4) *# pts not improved by at least 1 point on EDSS at 1 yr posttx:* Oriani (1990b) found that there was a sig benefit of HBOT for those having a longer course of tx but not for the shorter course (20 sessions vs >20 sessions) (longer course OR 0.19, 95% CI 0.05-0.73, *P*=0.02; shorter course OR 0.34, 95% CI 0.01-8,64, *P*=0.52) <u>*Harms*</u> *Incidence of visual disturbance during tx:* 4 trials (n=259) contributed to this outcome (Barnes 1985, Fischer 1983, Confavreux 1986, Wiles 1986); 71 (55%) pts suffered deterioration in visual acuity in the HBOT grp vs 3 (2.3%) in the sham grp (OR 24.87, 95% CI 1.44-428.5, *P*=0.03) (Chi2 15.33, df=3, *P*=0.002) (NNT=1, 95% CI 1-2) *Incidence of barotrauma:* 6 trials (n=349) contributed to this outcome (Barnes 1985, Fischer 1983, Confavreux 1986, Wood 1985, L'Hermitte 1986, Wiles 1986); 45 (24.5%) pts suffered an episode of barotrauma in the HBOT grp vs 15 (9.3%) in the sham grp (OR 2.94, 95% CI 0.62-13.91, *P*=0.17) (Chi2 12.3, df=5, *P*=0.031) *Incidence of oxygen toxicity:* No data	
Migraine/Cluster Headache					

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
Bennett et al. (2008) Cochrane Collaboration A systematic review to assess the safety and effectiveness of HBOT for treating and preventing migraine and cluster headaches Fife et al. (1992) (n=14) Hill (1992) (n=8) Di Sabato et al. (1993) (n=13) Myers and Myers (1995) (n=20) Wilson et al. (1998) (n=8) Eftedal et al. (2004) (n=40) Nilsson Remahl et al. (2002) (n=16)	*Included studies*: 7 *Search dates*: Up to May 2008 *Data sources:* CENTRAL, MEDLINE, Embase, CINAHL; DORCTIHM manually searched bibliographies for additional eligible trials; unpublished data sought *Inclusion criteria:* All RCTs examining the effectiveness of HBOT for migraine and cluster headache; pts of any age; headache classification followed the guideline of the International Headache Society, where possible *Eligible comparators:* Any standard tx regimen designed to prevent or terminate headaches or prevent recurrence, including combined txs, placebo, sham, and no tx *Quality assessment:* Based on criteria of Schultz (1995)	*Study design* 7 RCTs *Sample size* 119 (range 8-40) *# HBOT sessions* 1-40 *Comparators* Sham tx for acute migraine (n=5) Sham for cluster headache (n=2) *F/u* Immediately posttx to 48 hrs *Risk of bias* Generally medium to high risk of bias; 2 studies were presented as abstracts only	*HBOT dose (range)* 1.0-2.5 ATA for 20-70 mins *Outcomes* % pts w/ relief of acute migraine or cluster headaches; % pts requiring rescue medication; % pts w/ nausea and vomiting after tx; pain intensity score; # headache days/wk; % pts w/ sustained relief for 48 hrs; headache index *Harms* AEs related to HBOT; any other recorded AE	**Migraine** *% pts w/ relief* RR 5.97 (95% CI 1.46-24.38, *P*=0.01, I^2=43%); NNT=2 (95% CI 1-2) (Fife 1992; Hill 1992; Myers and Myers 1995) n=43, HBOT for 40-45 mins *% pts requiring rescue medication* Eftedal (2004): RR 0.84 (95% CI 0.64-1.11, *P*=0.23) *% pts w/ nausea and vomiting after tx* Eftedal (2004): RR 1.27 (95% CI 0.68-2.38, *P*=0.46) *Pain intensity score (immediately following tx)* Wilson (1998): Mean pain score, HBOT grp: 3.5 (SD 10.7) Mean pain score, control: 6.3 (SD 14) MD 2.8 (95% CI –4.69-10.29, *P*=0.46) *# headache d/wk* Eftedal (2004): MD during wk 1: –0.13 (95% CI –1.41-1.15, *P*=0.84) MD during wk 4: –0.25 (95% CI –1.52-1.02, *P*=0.70) MD during wk 8: –0.75 (95% CI –2.06-0.56, *P*=0.26) **Headache** *% pts w/ relief following 20 mins HBOT vs sham* Di Sabato (1993): HBOT: 86% (6/7 pts) Sham: 0% (0/6) RR in favor of HBOT 11.38, 95% CI 0.77-167.85, *P*=0.08	*Author's conclusions* There is some evidence that HBOT is effective for the termination of acute migraine in a general population of migraine sufferers. There is insufficient evidence that HBOT is effective for the tx of cluster headaches or as prevention against future headaches. *Limitations* Individual study quality was moderate to low; randomization was poorly described; primary outcomes were poorly reported; means and SD were poorly reported; sample sizes were very small; results should be interpreted w/ great caution. *Quality of review* Good

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
				% pts w/ sustained relief for 48 hrs Di Sabato (1993): HBOT: 86% (6/7 pts) Sham: 0% (0/6 pts) RR in favor of HBOT 11.38, 95% CI 0.77-167.85, *P*=0.08 *Headache index for effective tx* Nilsson Remahl (2002) HBOT grp: 36% (5/14) Sham: 38% (6/16) RR for 50% reduction in headache index w/ HBOT 0.98, 95% CI 0.40-2.41, *P*=0.97 <u>*Harms*</u> Myers and Myers (1995) noted no AEs; Eftedal (2004) reported 2 w/drawals due to claustrophobia, 1 upper respiratory chest infection and 1 w/drawal following a pathological chest x-ray; Di Sabato (1993) reported no AE	
Sensorineural Hearing Loss					
Bennett et al. (2007) Cochrane Collaboration An update of a 2005 systematic review to assess the evidence for the benefits of HBOT for treating ISSHL	*Included studies*: 7 *Search strategy:* Search dates: Up to July 2009 *Data sources:* Cochrane Ear, Nose and Throat Disorders Group Trials Register; CENTRAL; MEDLINE; Embase; CINAHL, DORCTHIM;	*Study design* 7 RCTs *Sample size* 392 (range 20-88) *# HBOT sessions* 10-25 *Comparators* Multimodal pharmacological	HBOT dose varied per tx session and between studies; range 1.5-2.5 ATA for 45-90 mins *Primary outcomes* Proportion of pts w/ >50% return of hearing at end of tx; proportion of pts w/ >25% return of hearing at end of tx; mean improvement in	<u>*Primary outcomes*</u> Cavallazzi 1996, Fattori 2001, Hoffman 1995a, Hoffman 1995b, Pilgramm 1985, Schwab 1998, Topuz 2004 **Acute ISSHL: Pure tone audiometric change in hearing** P*roportion of pts w/ >50% return of hearing at end of tx* 2 trials (n=114) (Cavallazzi 1996, Fattori 2001) reported on this outcome; no sig improvement	*Author's conclusions* There is limited evidence that HBOT improves hearing when applied as an early tx (w/in 2 wks) in ISSHL. Pts w/ acute ISSHL had sig improvements in hearing w/ the application of HBOT but clinical sig remains unclear; cautious interpretation is

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
Cavallazzi et al. (1996) (n=64) Fattori et al. (2001) (n=50) Hoffman et al. (1995a) (n=44) Hoffman et al. (1995b) (n=20) Pilgramm et al. (1985) (n=88) Schwab et al. (1998) (n=75) Topuz et al. (2004) (n=55)	manually searched bibliographies for additional eligible trials; unpublished data sought *Inclusion criteria:* RCTs or pseudo-RCTs that compared the effect of tx w/ HBOT w/ the effect of similar tx w/o HBOT; adults w/ acute-onset ISSHL of any duration; HBOT administered in a chamber above 1.2 ATA for txs between 30-120 mins at least once *Comparator:* Any std tx regimen designed to maximize hearing loss recovery or improve QOL for appropriate pts *Quality assessment:* Based on Cochrane risk of bias criteria	approach: n=4; vasodilator: n=1; sham: n=1; no tx; n=1 *F/u* Immediately posttx to 3 mos posttx *Duration of ISSHL pre-tx* Studies divided into 2 grps, acute ISSHL (0-6 mos), chronic ISSHL (up to 1 yr) *Degree of hearing loss* Required for entry by 2 studies (20 dB loss: in ≥1 frequency n=1; 30 dB loss in 3 frequencies: n=1); 3 studies stratified pts according to degree of hearing loss *Risk of bias (# studies)* Generally high risk of bias across studies	PTA as a % of baseline; proportion of pts w/ absolute improvement in PTA >20 dB; mean improvement in hearing over all frequencies (dB) *Secondary outcomes* ADL; subjective or objective improvements in depression or mood disturbance; hearing handicap inventory change *Subgrp analysis* Where appropriate data existed, subgrp analysis was considered based on: Time between onset and tx; etiology of ISSHL; HBOT dose; nature of comparative tx modalities; severity of hearing loss *Harms* Any AE	was found (RR of 50% improvement w/ HBOT 1.53, 95% CI 0.85-2.78, *P*=0.16, I^2=38.2%) *Proportion of pts w/ >25% return of hearing at end of tx* 2 trials (n=114) (Cavallazzi 1996, Fattori 2001) reported on this outcome; there was a sig improvement w/ HBOT (RR of 25% improvement w/ HBOT 1.39, 95% CI 1.05-1.84, *P*=0.02, I^2=0%); absolute risk difference was 22% (NNT for one extra good outcome 5 95% CI 3-20) *Mean improvement in PTA as a % of baseline* 1 trial (n=50) (Fattori 2001) reported on this outcome Sig mean improvement in PTA in HBOT grp: (61%) vs controls (24%) (WMD 37% in favor of HBOT, 95% CI 22%-53%) *Proportion of pts w/ absolute improvement in PTA >20 dB* 1 trial (n=20) (Hoffman 1995b) reported on this outcome; there was no sig improvement found w/ HBOT (RR for absolute improvement in PTA w/ HBOT 3.0, 95% CI 0.14-65.9, *P*=0.49 *Mean improvement in hearing over all frequencies (dB)* 4 trials (n=20) (Hoffman 1995b, Pilgramm 1985, Schwab 1998, Topuz 2004) reported on this outcome but only 2 (n=91) reported SD and contributed to the results (Pilgramm 1985, Topuz 2004); there was a sig improvement w/ HBOT (MD 15.6dB greater w/ HBOT, 95% CI 1.5-29.8, *P*=0.03, I^2=84%)	warranted and routine use is not justified. *Limitations* Meta-analysis was not appropriate or possible for several outcomes; risk of bias was generally high w/ poor reporting common among studies; particular risk of bias due to high spontaneous recovery from ISSHL coupled w/ varying entry times into studies. *Quality of review* Good

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
				Chronic ISSHL: Pure tone audiometric change in hearing *Proportion of pts w/ improvement in PTA* 1 trial (n=44) (Hoffman 1995a) reported on this outcome No sig difference between grps (RR for improvement w/ HBOT 0.64, 95% CI 0.30-1.33, *P*=0.23) *Mean improvement in hearing over all frequencies (dB)* 1 trial (n=51) (Pilgramm 1985) reported on this outcome No sig difference between grps (MD 1.4 dB in favor of HBOT grp, 95% CI –3.2-6.0, *P*=0.55) *Secondary outcomes* No trials reported data on secondary outcomes *Subgrp analysis* *Proportion of pts w/ >25% and 50% return of hearing at end of tx* Cavallazzi (1996) reported no sig difference in either a 25% or 50% improvement in hearing loss w/ HBOT by severity of loss RR for improvement of 50% w/ HBOT in mild hearing loss 1.54, 95% CI 0.79-2.55, *P*=0.24; severe hearing loss RR 1.07, 95% CI 0.29-3.88, *P*=0.92 RR for improvement of 25% w/ HBOT in mild hearing loss 1.32, 95% CI 0.86-2.02, *P*=0.21; severe hearing loss RR 1.28, 95% CI 0.56-2.91, *P*=0.56; *Mean improvement in hearing over all frequencies*	

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
				(dB) 2 studies (Pilgramm 1985, Topuz 2004) found a sig improvement in mean hearing w/ HBOT among those w/ severe hearing loss (n=14) at enrollment (MD 37.7dB, 95% CI 22.9-52.5, *P*<0.0001) but not among those w/ mild hearing loss (n=19) at enrollment (MD 0.2, 95% CI -10-10.4, *P*=0.97) <u>*Harms*</u> No trials reported AE in a systematic way. Pilgramm (1985) reported 6 w/drawals (3 pts w/ middle ear barotrauma, 3 pts w/ confinement anxiety)	
Harms Across Indications					
MSAC (2003) MSAC (Australia) Update of a 2001 report assessing HBOT for the tx of nonhealing wounds in nondiabetic pts and refractory soft tissue radiation injuries	*Included studies*: 8 *Search date:* 1966-2002 *Data sources:* Cochrane Library; CINAHL; MEDLINE; OVID; PreMEDLINE; Biological Abstracts; ACP Journal club; Embase; CancerLit (www.cancer.gov); National Guideline Clearinghouse; HBO	*Study design* 4 reviews, 4 observational studies *# HBOT sessions (range)* NR *F/u* NR *Risk of bias (# studies)* NR for harms	*Harms* Any AE or side effects of HBOT	<u>*HTNA and ANZHMG (2002)*</u> Incidence per # txs Persistent ocular changes: 1/112 (0.9%) Ear barotrauma: 1/170 (0.6%) Claustrophobia: 1/910 (0.1%) CNS seizures: 1/1548 (0.06%) Sinus barotrauma: 1/4864 (0.02%) Pulmonary O_2 toxicity: 1/6766 (0.01%) Pulmonary barotrauma: 0/15,475 (0%) Deaths: 0/21,033 (0%) <u>*Tibbles and Edelsberg (1996), Leach et al. (1998)*</u> Found that middle ear barotrauma and transient	*Author's conclusions* Most AEs are self limited and resolve after termination of tx. The most common AEs are myopia, barotrauma, claustrophobia, and O_2 toxicity; serious life threatening events are rare. *Limitations* Individual study quality

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
Included reviews Feldmeier (2001) Tibbles and Edelsberg (1996) Leach et al. (1998) MSAC (2001) **Included studies** HTNA and ANZHMG (2002) (n=21,033 tx sessions) Weaver and Churchill (2001) (13, 658 pts) Ohrui et al. (2002) (n=58,454 tx sessions) Plafki et al. (2000) (n=782 pts, 11,376 tx sessions)	evidence (www.hboevidence.com) *Inclusion criteria:* Nondiabetic pts w/ nonhealing refractory wounds having failed conventional tx; pts w/ soft tissue radiation injuries *Exclusion criteria:* Nonconsecutive case series; case reports; narrative reviews; abstracts; opinions *Comparator:* Any std tx regimen that does not involve HBOT; normobaric oxygen; placebo *Quality assessment tool:* NHS (UK) Center for Reviews and Dissemination list of criteria for evaluating validity of evidence for various study designs	data		myopia were the most common AEs associated w/ HBOT <u>MSAC (2001)</u> Reported progressive myopia was associated w/ prolonged, daily exposure to HBOT and was more common at higher pressures; reported seizures at a rate of 0.01% but did not seem to produce residual effects <u>Weaver and Churchill (2001)</u> 3/1028 female pts w/ cardiac disease and reduced ventricular ejection fractions developed pulmonary edema associated w/ HBOT; 2 recovered, 1 died <u>Ohrui et al. (2002)</u> *(incidence rate per 100 sessions)* Overall incidence of AE: 6.3% Ear pain: 4.8% Paranasal sinus pain: 0.86% Abdominal pain: 0.34% Hypoxia: 0.08% Hyperventilation: 0.08% Joint pain: 0.05% Toothache: 0.03% Other: 0.11% (unspecified) <u>Plafki et al. (2000)</u> Pain and/or discomfort during decompression: 216 events/ 11,376 tx sessions among 782 pts Tympanostomy tube placement: 12 events/ 11,376 tx sessions among 782 pts <u>Feldmeier (2001)</u> *(SR of 15 clinical studies)* Found that the weight of evidence suggests that	assessments were not performed for studies included under harms data. *Quality of review* Good

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
				HBOT does not increase the risk of primary cancer, metastatic growth, or recurrence and concluded that HBOT should not be w/held due to concerns regarding the likelihood of tumor recurrence in pts where HBOT is indicated	
Weaver (2011) LDS Hospital; University of Utah School of Medicine, Salt Lake City, UT A systematic review to assess HBOT for critically ill, intubated, mechanically ventilated pts Lo et al. (2005) (n=199) Weaver et al. (2006) (n=182) Rockswold et al. (2010) (n=69)	*Included studies*: 3 *Search dates:* NR *Data sources:* MEDLINE; research repository of the Rubicon Foundation to find publications not indexed in PubMed as well as abstracts and reports presented at scientific meetings; clinical trial registry *Inclusion criteria:* Critically ill, intubated, mechanically ventilated pts; *Quality assessment:* NR	*Study design* All observational *Lo et al. (2005):* 199 pts from 1981-2003; pts were tx'd for necrotizing infections, carbon monoxide poisoning, compromised surgical flaps/grafts, and acute arterial ischemia Weaver et al. (2006): 182 pts (154 w/ outcome data) w/ necrotizing fasciitis, carbon monoxide poisoning, crush injury, gangrene, arterial gas embolism, mucormycosis, arterial insufficiency, failing flaps, osteomyelitis, or radiation necrosis, tx w/ HBOT from 1986-2006	*Harms:* any reported harms	*Lo et al. (2005):* No HBOT-related mortality *Weaver et al. (2006):* Mortality (from their disease or w/drawal of support): 27/154 pts (18%) Complications necessitating decompression from chamber: 35/1281 sessions (2.7%) *Rockswold et al. (2010):* No evidence of O_2 toxicity	*Author's conclusions* Critically ill pts can be safely tx'd w/ HBOT once important safety protocols are followed. *Limitations* No assessment of risk of bias of included studies; poor reporting of individual study characteristics. *Quality of review* Poor

Systematic Review/HTA (Author and Date) Primary Data (Author and Date)	Systematic Review Characteristics	Individual Study Characteristics	Treatment Protocol Outcome(s)	Key Findings (Benefits and Harms)	Conclusions/ Limitations Quality of SR/HTA
		Rockswold et al. (2010): 69 pts w/ severe TBI			

Appendix IV. Summary of Key Findings from Primary Data Studies

KQ1, KQ1a, KQ2, and KQ3

Key: AE(s), adverse event(s); ATA, atmosphere absolute; BP, blood pressure; CSF, cerebral spinal fluid; dB, decibel; df, degrees of freedom; ESWT , extracorporeal shock wave technology; F, F statistic; f/u, follow-up; GCS, Glasgow Coma Scale; grp(s), group(s); Gy, gray; HA, hyaluronic acid; HbA1c, hemoglobin A1c; HBOT, hyperbaric oxygen therapy; HR, heart rate; ICP, intracranial pressure; ITT, intention to treat; kHz, kilohertz; LNNB, Luria-Nebraska Neuropsychological Battery; LRTI, late radiation tissue injury; MD, mean difference; MEBT, middle ear barotrauma; mm Hg, millimeter of mercury; NA, not available; NBH, normobaric hyperoxia; NR, not reported; NS, not statistically significant; PO_2, partial pressure of oxygen; pt(s), patient(s); RCT, randomized controlled trial; SD, standard deviation; SSHL, sensorineural hearing loss; std, standard; sx, symptom(s); TBI, traumatic brain injury; tx, treatment (or therapy); tx'd, treated; VAS, visual analog scale

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
Cross-cutting				
Al-Waili et al. (2006) Mount Vernon Hospital, Mount Vernon, NY Prospective cohort study to investigate the influences of HBOT on BP, HR, and blood glucose among pts w/ a variety of indications F/u: NA Funding source: NR	n=41 (mean age 61 yrs, range 31-86; 34% female) 4 grps (hypertensive pts, diabetic pts, diabetic and hypertensive pts, pts w/o diabetes or hypertension) HBOT indications Osteomyelitis n=16 (39%) Osteoradionecrosis n=6 (15%) Necrotizing fasciitis n=1 (2%) Compromised skin graft n=6 (15%) Chronic ulcer n=9 (22%) Nonhealing wound n=4 (10%) *Inclusion criteria:* Pts referred for HBOT for a variety of indications *Exclusion criteria:* NR	*Tx protocol* Monoplace chamber, 100% O_2 2.0-2.5 ATA for 60-90 mins according to indication; 1 session/day *# sessions/pt (range)* 15-30/pt *Total # sessions* 700 *Outcomes* Systolic BP, diastolic BP, HR *Harms* Any reported AEs	**Total pts (n=41)** *Systolic BP (mm Hg) mean (SD)* Prior to tx: 127 (15.2) Posttx (w/in 10 mins): 134 (10.6) *P*=0.001 *Diastolic BP (mm Hg) mean (SD)* Prior to tx: 72.9 (8.5) Posttx (w/in 10 mins): 81.8 (8.6) *P*<0.001 *HR (beats/min) mean (SD)* Prior to tx: 82.7 (11.7) Posttx (w/in 10 mins): 69.3 (10.9) *P*=0.001 *Blood sugar (mg/dL) mean (SD)* Prior to tx: 231 (95) Posttx (w/in 10 mins): 179 (85.8) *P*<0.001 **Diabetes (n=11)** *Systolic BP (mm Hg) mean (SD)* Prior to tx: 125 (15) Posttx (w/in 10 mins): 142 (17.2) *P*<0.001 *Diastolic BP (mm Hg) mean (SD)*	*Author's conclusions* Underlying diseases and types of medical tx significantly influence the effects of HBOT on vital signs. Beta-blockers should be avoided in pts scheduled for HBOT; diabetic pts on oral anti-diabetics should be fed prior to HBOT if their blood sugars are <120 mg/dL; diabetic pts tx'd w/ insulin should be fed prior to HBOT when blood sugars are <170 mg/dL. HBOT causes a significant elevation in BP and significant drop in HR; BP was higher in those hypertensive pts w/ diabetes compared w/ those w/o diabetes; greater elevations in BP and drop in HR was seen among pts w/ both diabetes and hypertension compared w/

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
			Prior to tx: 71.8 (8.81) Posttx (w/in 10 mins): 80.4 (7.8) *P*<0.001 *HR (beats/min) mean (SD)* Prior to tx: 85.2 (12.2) Posttx (w/in 10 mins): 71.4 (12.1) *P*<0.001 *Blood sugar (mg/dL) mean (SD)* Prior to tx: 236 (86.5) Posttx (w/in 10 mins): 185 (76) *P*=0.001 **Hypertension (n=6)** *Systolic BP (mm Hg) mean (SD)* Prior to tx: 127 (SD 12.9) Posttx (w/in 10 mins): 141 (SD 10.9) *P*=0.001 *Diastolic BP (mm Hg) mean (SD)* Prior to tx: 73.3 (8.03) Posttx (w/in 10 mins): 83.4 (7.9) *P*<0.001 *HR (beats/min) mean (SD)* Prior to tx: 80.2 (10.5) Posttx (w/in 10 mins): 68.1 (10.9) *P*=0.001 **Diabetes and hypertension (n=12)** *Systolic BP (mm Hg) mean (SD)* Prior to tx: 136 (15.7) Posttx (w/in 10 mins): 160 (22.2) *P*=0.001 *Diastolic BP (mm Hg) mean (SD)* Prior to tx: 74.1 (10.2) Posttx (w/in 10 mins): 83.8 (10.1) *P*=0.001 *HR (beats/min) mean (SD)* Prior to tx: 83.5 (13.5)	other grps; diabetes causes a greater elevation in BP after tx compared w/ hypertensive pts, nonhypertensive pts and nondiabetic pts; pts w/ both hypertension and diabetes showed a greater reduction in HR after tx compared w/ other grps; beta blockers cause a greater elevation in BP and decrease in and blood sugars compared w/ other medications; diabetes affects hypertension control and augments the affects of HBOT on BP and HR; coexisting diabetes and BP further exaggerate the effects of HBOT on BP and HR; a significant elevation in BP was seen in those w/ basal systolic BP >140. *Limitations* Small sample size, differences in HBOT protocol between pts; no randomization; no mention of blinding; risk of selection bias is high; inconsistencies between text and tables. *Quality* Poor

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
			Posttx (w/in 10 mins): 72 (12.2) *P*=0.001 *Blood sugar (mg/dL) mean (SD)* Prior to tx: 234 (102) Posttx (w/in 10 mins): 186 (94.7) *P*=0.001 **No diabetes or hypertension (n=12)** *Systolic BP (mm Hg) mean (SD)* Prior to tx: 123 (12.1) Posttx (w/in 10 mins): 136 (13.4) *P*=0.001 *Diastolic BP (mm Hg) mean (SD)* Prior to tx: 72.4 (6.8) Posttx (w/in 10 mins): 80.8 (7.3) *P*=0.001 *HR (beats/min) mean (SD)* Prior to tx: 82.3 (9.8) Posttx (w/in 10 mins): 67.8 (9.1) *P*<0.001 **Harms** 2 pts w/ diabetes developed hypoglycemic sx during tx; 1 pt developed an asthmatic attack during tx; 1 pt w/ hypertension developed anxiety, severe headache and elevated BP; 1 pt developed ocular complications; 2 pts developed ear pain	
Toklu et al. (2008) Istanbul University, Istanbul, Turkey Questionnaire to determine how pts w/ radiological evidence of pulmonary plebs or bullae were tx'd in	n=266 questionnaires e-mailed Q1: Do you apply HBOT to the pts having radiological evident of pulmonary blebs or bullae? Q2: What type of chamber (multiplace/monoplace) do you use? Q3: What is the total # HBOT sessions done in your center	*Tx protocol* NR *# sessions/pt (range)* NR *Total # sessions* 2 M *Outcomes*	Response rate: 36.8% (98/266) Centers who do not treat pts w/ air cysts in their lungs: 33.7% Centers who treat pts w/ air lung cysts: 66.3% Of the centers, which treat pts w/ air cysts in their lungs: 30.7% reported using HBOT only for emergent cases such as gas gangrene or decompression	*Author's conclusions* A significant proportion of centers apply HBOT even in the presence of air cysts in the lungs. The incidence of lung barotrauma is very low. HBOT may be administered w/o screening for air trapping lesions, if there is no clinical indication of a current lung

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
different HBOT centers and the prevalence of pulmonary barotrauma F/u: NA Time frame: NR Funding source: NR	approximately? Q4: Did you have any pulmonary barotrauma case during HBO treatment session? Q5: Do you radiologically screen the pts who have a history of lung disease?	Incidence of pulmonary barotrauma among pats w/ air cyst in their lungs	sickness); 23% applied HBO after careful consideration of benefits and harms; 69.2% use multiplace chambers where medical intervention is possible *Incidence of pulmonary barotrauma*: 0.00045% (9/2M data from 7 centers)	disease. *Limitations* This was a survey of behavior w/ no control or active comparison. The risk of bias is particularly high if respondents differed significantly from nonrespondents. *Quality* Poor
Diabetes				
Wang et al. (2011) Chang Gung University College of Medicine, Taiwan, China RCT comparing HBOT w/ ESWT for the tx of chronic diabetic foot ulcers F/u: HBOT grp, 11.1 mos, range 3-18; ESWT grp, 13.5 mos, range 3-18 Funding source: Chang Gun Research Fund	n=86 (93 foot ulcers) ESWT grp: n=41 (46 feet); demographic data based on n=39 (age 60.51 yrs, range 20-81; median ulcer size 4, range 1.5-9; median duration of ulcer 6 mos, range 3-16; right/left 17/27; mean HBA1c 8.76, SD 2.23, range 5.6-12.4) HBOT grp: n=45 (47 feet); demographic data based on n=38 (age 62.45 yrs, range 23-88; median ulcer size 7, range 2-12; median duration of ulcer 6 mos, range 6-10; right/left 24/16; mean HBA1c 8.09, SD 1.76, range 5.4-12.1) *Inclusion criteria*: Chronic nonhealing diabetic foot ulcers for >3 mos	*Tx protocol* ESWT: Dose was dependent on the ulcer size w/ # impulses equal to the tx area in cm^2 × 8, w/ a minimum of 500 impulses at energy setting E2 at a rate of 4 shocks/sec; tx given 2×/wk for 3 wks for total of 6 txs; pre-ESWT wound care protocol was resumed following tx HBOT: Multiplace chamber at 2.5 ATA; 100% O_2 for a total of 90 mins/tx (includes time for gradual increase from 1-2. AT and 5-min break); performed daily 5×/wk for total of 20 sessions; similar posttx wound care	*Ulcer status (by # feet)* 1st course of tx Completely healed ESWT: 57% (24/44) HBOT: 25% (10/40) *P*=0.003 *≥50% improvement* ESWT: 32% (14/44) HBOT: 15% (6/40) *P*=0.071 *Unchanged* ESWT: 11% (5/44) HBOT: 60% (24/40) *P*<0.001 *Worsened* ESWT: 0 HBOT: 0 **2nd course of tx** Completely healed	*Author's conclusions* ESWT is more effective than HBOT in the tx of chronic nonhealing diabetic foot ulcers; ESWT showed better blood flow perfusion rate and cell activity and decreased cell apoptosis relative to HBOT. No baseline differences in demographic characteristics; power analysis was performed. *Limitations* No blinding, no ITT analysis (9 pts lost to f/u); small sample size; length of f/u was relatively short. *COI* One author served as a member of the scientific advisory board of Sanuwave until November

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
	Exclusion criteria: Cardiac arrhythmia or a pacemaker, pregnancy, skeletal immaturity, pts w/ malignancy, pts lacking complete f/u data *Lost-to f/u:* HBOT grp: 7 ESWT grp: 2	protocol as the ESWT grp Tissue viability assessed using local blood flow perfusion scan and histopathological exam performed on biopsy specimens pretx and posttx *Outcomes* Ulcer status following 1st and 2nd course of tx (completely healed; ≥50% improvement; unchanged; worsened); blood flow perfusion *Harms* Any reported complications	ESWT: 50% (7/14) HBOT: 6% (1/17) *P*=0.005 <u>≥50% improvement</u> ESWT: 43% (6/14) HBOT: 47% (8/17) *P*=0.815 <u>Unchanged</u> ESWT: 7% (1/14) HBOT: 47% (8/17) *P*=0.015 <u>Worsened</u> ESWT: 0 HBOT: 0 <u>*Blood flow perfusion**</u> *Before tx (range)* ESWT: 0.48 (0.32-0.64) HBOT: 0.59 (0.5-0.63) *P*1<0.001 *P*2=0.245 *After tx* ESWT: 0.61 (0.4-0.79) HBOT: 0.50 (0.11-0.53) *P*1=0.916 *P*2=0.002 **P*1 w/in grp comparison; *P*2 between grp comparison Harms HBOT grp: 4 pts developed ear barotrauma and sinus pain resolving spontaneously after release of chamber pressure ESWT grp: No reported complications	2012. *Quality* Poor

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
LRTI				
Shao et al. (2012) Shanghai Jiaotong University, Shanghai, China RCT to compare HBOT w/ intravesical HA for the tx of radiation induced hemorrhagic cystitis F/u: Every 6, 12, and 18 mos Funding source: NR	n=36 HBOT grp: n=20 (median age 60, range 39-77) HA grp: n=16 (median age 59, range 46-74) *Original cancer (radiation dose):* HBOT grp Cervical: 7 (50-60 Gy) Prostatic: 4 (55-70 Gy) Rectal: 9 (45-60 Gy) HA grp: Cervical: 5 (50-60 Gy) Prostatic: 4 (55-70 Gy) Rectal: 7 (45-60 Gy) *Degree of hematuria:* HBOT grp I: 0/20 II: 10/20 III: 10/20 IV: 0/20 HA grp I: 0/16 II: 6/16 III: 10/16 IV: 0/16 *Bladder irrigation:* HBOT grp: 3/20 HA grp: 3/16 *Inclusion criteria*: Pts w/	*Tx protocol* HBOT grp: 100% O_2 at 2.5 ATA for 60 mins, once/daily, 7 days/wk for at least 1 mo HA grp: 40 mg HA slowly instilled into the bladder and clamped for 20 mins, once weekly for 1 mo then monthly in following 2 mos *Outcome measures* Sx of hematuria, frequency of voiding and VAS of pelvic pain (range 0-10) were evaluated pretx and posttx (complete response defined as day at which all sx disappeared; partial response defined as disappearance of clots but w/ persistence of hematuria)	No significant differences between grps based on age, gender, or primary disease Improvement rate *Complete recovery at 6 mos* HBOT grp: 75% (15/20) HA grp: 87.5% (14/16) *P*=NS *Complete recovery at 12 mos* HBOT grp: 50% (10/20) HA grp: 75% (12/16) *P*=NS Complete recovery at 18 mos HBOT grp: 45% (9/20) HA grp: 50% (8/16) *P*=NS *Partial recovery at 6 mos* HBOT grp: 95% (19/20) HA grp: 100% (16/16) *P*=NS *Partial recovery at 12 mos* HBOT grp: 85% (17/20) HA grp: 94% (15/16) *P*=NS *Partial recovery at 18 mos* HBOT grp: 75% (15/20) HA grp: 75% (12/16) *P*=NS *Voiding frequency* Voids/day (change from baseline, SD) HBOT grp	*Author's conclusions* Both HA and HBOT were effective in treating radiation induced hemorrhagic cystitis; there was a decrease in voiding frequency in both grps 6 mos posttx but only significant in the HA grp at 12 mos; an improvement in VAS was seen in both grps through 18 mos. *Limitations* Small sample size; blinding NR; allocation concealment NR. *Quality* Fair

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
	radiation induced hemorrhagic cystitis defined as the presence of macroscopic hematuria in the absence of other conditions such as gynecological-related bleeding, nephrolithiasis and/or bacterial or fungal infection of the lower urinary tract; pts having undergone radiotherapy for cervical cancer, rectal cancer, or prostate cancer from November 2004 – December 2008 *Exclusion criteria:* Bladder cancer		6 mos: –1.2 (1.06) *P*<0.01 12 mos: –0.15 (0.99) *P*=NS 18 mos: 0.2 (0.83) *P*=NS HA grp 6 mos: –2.9 (1.7) *P*<0.01 12 mos: –1.5 (1.4) *P*<0.01 18 mos: –0.18 (0.54) *P*=NS *Change in VAS* VAS (change from baseline, SD) HBOT grp 6 mos: –0.9 (0.79) *P*<0.01 12 mos: –0.9 (1.02) *P*<0.01 18 mos: –1.15 (1.22) *P*<0.01 HA grp 6 mos: –0.88 (1.41) *P*<0.05 12 mos: –1.31 (1.3) *P*<0.01 18 mos: –1.5 (1.21) *P*<0.01	
Brain Injury				
Golden et al. (2006) University of Florida; Nova Southeastern University; Ocean Hyperbaric Center, Ft. Lauderdale, FL Observational pre-post test study to investigate the effectiveness of HBOT vs controls to improve neuropsychological function after chronic brain injury in children and adults	Study 1: Children (n=63) Study 2: Adults (n=63) Study 1: HBOT grp: n-21 (mean age 55.43 mos, SD 46.3; yrs of education 1.19, SD 2.73; female 48%; race 100% Caucasian; HBOT grp received 28.81 SD 15.27 txs over 27.29 SD 29.18 days) Chronic brain-injured controls: n=21 (mean age 59.67 mos, SD 43.24; yrs of education 1.1, SD 2.63; female 43%) Normal controls: n=21 (mean age 67 mos, SD 43; yrs of	*Tx protocol* NR **Outcome measures** Study 1 Vineland Adaptive Behavior Scale evaluating 4 areas of general function: 1) daily living skills 2) communication 3) social skills 4) motor skills Differential effectiveness: Results stratified according to respondents vs nonrespondents Study 2	Study 1 No baseline differences for age, gender, or education Total change in general function (mean SD) HBOT: 43.57 (31.45) Brain-injured controls: 3.71 (5.99) Normal controls: 21.88 (7.81) *P*=0.000 Daily living skills (mean change SD) HBOT: 10.81 (8.04) Brain-injured controls: 1.19 (2.79) Normal controls: 5.84 (5.08) *P*=0.000 Communication (mean change SD) HBOT: 9.71 (7.73) Brain-injured controls: 1.48 (1.72) Normal controls: 6.3 (2.83) F(2,56)=15.25, *P*=0.000	*Author's conclusions* Both studies demonstrated clear improvements in cognitive performance among pts tx'd w/ HBOT vs either control grp. Study 1 There appears to be a dose-response among child respondents but not among nonrespondents. Study 2 There is a moderate dose response curve among adults at this tx level; # txs appear to be more important than the

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
F/u: 4-8 wks posttx Funding source: NR	education 1.57, SD 1.99; female 43%) Type of chronic brain injury: Cerebral palsy 29; stroke 12%, TBI 26%, Lyme disease 7%, anoxic ischemic encephalopathy 17%, other 9% <u>Study 2:</u> HBOT grp: n-21 (mean age 40.76 yrs, SD 17.8; yrs of education 12.52, SD 1.78; female 24%; race 100% Caucasian; HBOTs received 35.38 SD 18.17 txs over 34.52, SD 17.7 days) Chronic brain-injured controls: n=21 (mean age 39.19 yrs, SD 16; yrs of education 12.14, SD 2.69; female 19%) Normal controls: n=21 (mean age 37.48 yrs, SD 12.1; yrs of education 13.52, SD 2.4; female 29%) Type of chronic brain injury: Head trauma (26%); hypoxia (7%); anoxia (21%); stroke (26%); other (20%) *Inclusion criteria*: Pts w/ referral for HBOT because of chronic brain injury; reported (by family) as having a static level of functioning for at least 1 yr despite other txs; adults had chronic brain injury for at least 2 yrs	Stroop (consists of 3 pages, the W page consists of the words RED, GREEN and BLUE, the C page consists of color patches, the pt must read pages W and C as fast as possible for 30s; the CW page consists of the words in W printed in the colors on C in such a way that the words and colors do not match, the pt must name the color ignoring the word the ink spells) LNNB (consisting of 4 scales: motor, tactile, receptive language, and expressive language) Word fluency: (pts asked to generate as many words as possible from 5 categories Logical memory (immediate recall and delayed recall measured from the reading of 2 stories) Total score : the sum of number correct	Social skills (mean change SD) HBOT: 13.19 (12.68) Brain-injured controls: 0.95 (3.25) Normal controls: 5.97 (4.43) F(2,56)=12.48, *P*=0.000 Motor skills (mean change SD) HBOT: 9.86 (11.42) Brain-injured controls: 0.1 (2.91) Normal controls: 3.77 (6.42) F(2,56)=8.50, *P*=0.001 <u>Subpopulations</u> A dose response among respondents but not non-respondents Non-respondents: Correlation between # txs and change scores: 0.098 (range –0.28-0.18) Respondents: Correlation between # txs and change scores: 0.47 (range 0.16-0.53) <u>Study 2</u> Total (MD score, SD) HBOT: 62.73 (42.01) Brain-injured controls: 1.13 (13.27) Normal controls: 8.10 (6.69) F(2,56)=35.97, *P*<0.01 LNNB motor (MD score, SD) HBOT: 8.88 (8.12) Brain-injured controls: –1.85 (12.74) Normal controls: 0.97 (1.53) F(2,56)=8.54, *P*<0.01 LNNB tactile (MD score, SD) HBOT: 3.48 (6.26) Brain-injured controls: 0.54 (0.52) Normal controls: 0.71 (0.72) F(2,56)=4.91, *P*=NS LNNB receptive (MD score, SD) HBOT: 5.53 (9.26)	duration of each tx. *Limitations* Studies 1 and 2: No control grp; no blinding; HBOT protocol was not provided; HBOT grp appeared to have more severe injury pretx; risk of parental bias due to parent reporting for the child study tests. *COI* NR *Quality* Poor

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
	Exclusion criteria: NR		Brain-injured controls: 0.88 (0.87)) Normal controls: 1.19 (1.10) F(2,56)=5.23, *P*<0.01 LNNB expressive (MD score, SD) HBOT: 12.24 (16.38) Brain-injured controls: 0.88 (1.26) Normal controls: 1.84 (2.18) F(2,56)=9.83, *P*<0.01 Stroop word (MD score, SD) HBOT: 7.52 (11.81) Brain-injured controls: 0.1 (1.22) Normal controls: 0.52 (2.46) F(2,56)=6.36, *P*<0.01 Stroop color (MD score, SD) HBOT: 9.67 (8.45) Brain-injured controls: -0.43 (1.21) Normal controls: 0.71 (1.35) F(2,56)=23.65, *P*<0.01 Stroop word-color (MD score, SD) HBOT: 7.19 (8.71) Brain-injured controls: -0.33 (1.39) Normal controls: 1.71 (1.52) F(2,56)=18.14, *P*<0.01 Verbal fluency (MD score, SD) HBOT: 3.35 (4.98) Brain-injured controls: -0.19 (1.29) Normal controls: 0.43 (2.06) F(2,56)=7.90, *P*<0.01 Logical memory recall (MD score, SD) HBOT: 2.71 (3.09) Brain-injured controls: 0.67 (2.99) Normal controls: -0.48 (3.28) F(2,56)=6.81, *P*<0.01 Logical memory delay(MD score, SD) HBOT: 3.90 (2.76) Brain-injured controls: 0.86 (1.56) Normal controls: 0.48 (1.97)	

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
			F(2,56)=21.08, *P*<0.01 # txs and duration of txs correlated w/ each other 0.287 (df=62, *P*<0.05); duration of tx only correlated w/ verbal fluency	
Rockswold et al. (2010) University of Minnesota; Minneapolis Medical Research Foundation, Minneapolis, MN RCT to compare the effect of hyperbaric w/ NBH on cerebral metabolism, ICP, and O_2 toxicity in severe TBI F/u: Immediately posttx Funding source: Minneapolis Medical Research Foundation Bridging Fund, National Institute of Neurological Disorders and Stroke Hyperbaric and Normobaric in severe brain injury grant, private donation from the West Family foundation	n=69 (mean age 35 yrs, male female ratio 58:11) *Baseline characteristics:* Average entry GCS score of 5.8; male female ratio 6:1; 58% had sustained multiple traumas; 48% had intracranial hypertension *Inclusion criteria:* All closed-head trauma victims w/ GCS score 3-8 after resuscitation, w/o effects from paralysis, sedation, alcohol or street drugs; pts were entered into the study w/in 24 hrs of injury or after having been admitted for mild or moderate TBI and deteriorating w/in 48 hrs computerized tomography scan scores were ≥II *Exclusion criteria:* GCS score >8; severe pulmonary injury; hx of severe pulmonary disease; unstable fractures; fixed coagulopathy; pregnancy; severe mental retardation; prior severe brain injury or stroke; high velocity	*Tx protocol* All pts received std TBI care paralleling the Brain Trauma Foundation's guidelines, including receiving prophylactic phenytoin sodium; multiplcae chamber (n=17), monoplace chamber (n=9) HBOT grp: HBOT at 1.5 ATA for 60 mins (n=26) once daily × 3 days NBH grp: 3 hrs of 100% fraction of inspired O_2 at 1 ATA (n=21) Control: Std care (n=22) *Outcome measures (of interest)* ICP *Harms* O_2 toxicity, determined by measuring ventricular CSF F2-isoprostane *Outcome measures (not of interest)*	No statistically significant differences between grps in relation to baseline characteristics or CT scores at study entry ICP. There was a significant decrease in intracranial pressure after HBOT in comparison to std care (*P*=0.001). *O_2 toxicity* Levels of ventricular CSF F2-isoprostane did not significantly change from pretx to posttx, or over time for the HBOT grp in comparison w/ controls, *P*=NS.	*Author's conclusions* There was a significant decrease in intracranial pressure after HBOT in comparison to NBH or std care; there was no evidence of cerebral or pulmonary O_2 toxicity w/ HBOT. Data for the following conclusions were not abstracted: HBOT had a significantly greater posttx effect than NBH on oxidative cerebral metabolism; a critical brain tissue PO_2 level of 200 mm Hg seemed important to achieve a robust positive effect; HBOT had a posttx effect lasting at least 6 hrs meaning that tx can be delivered intermittently reducing the chance of O_2 toxicity. *Limitations* This was not a clinical outcome trial because dosing was not made at therapeutic intervals; outcomes were primarily surrogate clinical outcomes (Glasgow outcome score was not calculated posttx); no long term outcomes; no blinding

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
	penetrating injury to the head; multiple organ failure	Cerebral metabolic measures, critical levels of brain tissue, PO_2		noted. *COI* NR *Quality* Fair
Cerebral Palsy				
Muller-Bolla et al. (2006) McGill University, Montreal, Canada; Universite Nice-Sophia-Antipolis, Nice, France RCT looking at the efficacy of HBOT for children w/ cerebral palsy; this paper reports the side effects of HBOT F/u: 8 wks Time frame: NR Funding source: Fond de la Recherche en Sante au Quebec	n=111 (mean age 7.2 yrs, range 3-12) *Inclusion criteria:* Documented diagnosis of CP w/ hx of hypoxia in the perinatal period; age 3-12 yrs; motor developmental age 6 mos – 4 yrs; psychological development age ≥24 mos *Exclusion criteria:* Postneonatal onset of cerebral palsy; other causes of encephalopathy; children who had one recent episode (w/in 1 mo) of acute otitis or those w/ chronic otitis (3 episodes or more w/in the previous yr); those w/ any condition that put them at risk of complications of HBOT (asthma, convulsions); children w/ behavioral problems or those recently treated w/ botulinum toxin or orthopedic surgery (w/in the past 6 mos) or dorsal rhizotomy w/in the	*Tx protocol* HBOT grp: Monoplace or multichamber; 100% O_2 at 1.75 ATA for 60 mins Control: Air at 1.3 ATA *# sessions/pt* 40/pt over 2 mos *Harms* All AEs *Analysis* ITT	<u>*HBOT-related MEBT*</u> HBOT grp: 50% (28.57) Control grp: 27.8% (15/54) RR 1.5 (95% CI 1.1-2.2, *P*=0.02) <u>*% children w/ at least 1 event*</u> *Myringotomy w/out barotrauma* HBOT grp 5.4, control 0; pharyngitis, HBOT grp 28.6, control 14.8; ear pain, HBOT grp 14.3, control13; otitis 7.1, control 7.4; fever, HBOT grp 5.4, control 5.6; dyspepsia, HBOT grp 1.8, control 7.4; myringotomy tube problems, HBOT grp 5.4, control 1.9; vomiting, HBOT grp 3.6, control 3.7 No neurological or pulmonary manifestations of O_2 toxicity were noted; visual changes were not noted.	*Author's conclusions* HBOT using low hyperbaric pressure conditions were generally well tolerated; main AE was barotrauma; occurrence of MEBT did not differ according to baseline characteristics. *Limitations* O_2 pressure was low in HBOT grp; children in the control grp also received pressurized air (1.3 vs 1.75 ATA in tx grp); small sample size; AE may be higher in a more generalized population of children w/ cerebral palsy. *Quality* Good

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
	past 2 yrs; previous exposure to HBOT			
Sensorineural Hearing Loss				
Muzzi et al. (2010) Case series to investigate HBOT as salvage tx for SSHL F/u: 6 mos Timeframe: November 2003 – February 2008 Funding source: NR	n=19 (mean age 46.68 yrs, range 29-67; female 53%, affected ear 53% in left ear) *Inclusion criteria*: SSHL is defined as hearing deterioration of at least 30 dB over ≥3 contiguous frequencies occurring w/in 3 days; no improvement in pure tone hearing thresholds following first-line medical tx *Exclusion criteria*: Non-bleeders W/drawal: n=3 (before 15 sessions)	*Tx protocol* Multiplace chamber; 2.5 ATA 90 mins and free air inhalation for 30 mins, once/daily for 5 consecutive days, for a median of 28 sessions (interquartile distance 15; range 8-46 sessions) *Outcome measures* Hearing improvement (measured as pure tone hearing thresholds across low (0.25 and 0.5 kHz) middle (0.5 and 1 kHz) and high (4 and 8 kHz) frequencies) *Harms* Any reported AE *Subpopulations outcomes* Age (<50 yrs vs ≥50 yrs); therapeutic delay, (<15 days vs ≥15 days); # HBOT sessions (<30 vs ≥30)	*Overall hearing improvements (average across frequencies)* Absolute improvement (dB): 8.64 Relative improvement (%): 16 Harms None reported *Subpopulation results* Age (<50 yrs) (n=11) Absolute improvement (dB): 4.47 Relative improvement (%): 8 Age (≥50 yrs) (n=8) Absolute improvement (dB): 14.38 Relative improvement (%): 20 *P*=0.037 at low frequencies, *P*=NS at middle and high frequencies Therapeutic delay (<15 days) (n=6) Absolute improvement (dB): 11.67 Relative improvement (%): 17 Therapeutic delay (>15 days, ≤30 days) (n=5) Absolute improvement (dB): 10.83 Relative improvement (%): 16 Therapeutic delay (>30 days) (n=8)	*Author's conclusions* When common treatments for sudden SSHL fail, HBOT leads to an improvement in pure tone hearing thresholds, particularly for low frequencies; age >50 yrs was a positive prognostic factor for recovery at low frequencies. The number of HBOT sessions did not significantly affect hearing outcome; there was no difference in outcome if tx was <15 days of presentation or between 15-30 days. Results should be interpreted cautiously given the preliminary nature of the study design. *Limitations* No control, small sample size, risk of selection bias. *Quality* Poor

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
			Absolute improvement (dB): 5 Relative improvement (%): 10 *P*=0.026 at low frequencies, *P*=0.006 at middle frequencies # HBOT sessions (<30 sessions) (n=10) Absolute improvement (dB): 6.5 Relative improvement (%): 13 # HBOT sessions (≥30 sessions) (n=9) Absolute improvement (dB): 11.02 Relative improvement (%): 15 *P*=NS	
Cekin et al. (2009) Haydarpasa Training Hospital, Istanbul, Turkey RCT to investigate the effectiveness of HBOT in the management of sudden hearing loss F/u: NR Timeframe: 1994-2006 Funding source: NR	n=57 pts (59 ears) HBOT grp: n=36 (38 ears) (mean age 46.8 yrs, range 18-82; 33% female) Control : n=21 (mean age 44.5 yrs, range 20-75; 38% female) *Baseline characteristics:* Tinnitus: HBOT grp 14 pts, control 6 pts; smoking HBOT grp 36%, control 38%; hypertension HBOT 5.5%, control 4.8%; hx hypertension HBOT 25%, control 33.33%; viral infection 0%; cranial CT pathology HBOT 3%, control 0%; mean triglycerides HBOT 185 mg/dL, control 178 mg/dL *Inclusion criteria*: Hearing loss defined as loss of minimum of 30 dB in ≥3 frequencies occurring w/in period of 3 days	*Tx protocol* All pts received steroids (prednisolone starting at 1 mg/kg reducing over 3 wks) and famotidine (40 mg once daily) HBOT: Multiplace chamber at 2.5 ATA; 100% O_2 for a total of 90 mins/tx once daily for 10 days Control: Received the same std steroid tx w/ no HBOT *Outcome measures* Pure tone audiography: Complete recovery (improvement >50 dB) moderate recovery (improved 10-50 dB) or no recovery (improved <10 dB))	**Overall success rate (complete or moderate recovery)** HBOT: 78.95% Control: 71.3% *P*=NS **Hearing recovery (mean pure tone audiogram/dB)** <u>Pretx</u> *HBOT* Complete: 74.3 Moderate: 93.1 None: 89.7 *Control* Complete: 94.0 Moderate: 98.5 None: 97.5 <u>Posttx</u> *HBOT* Complete: 23.5 Moderate: 52.2 None: 82.7 *Control* Complete: 28.5 Moderate: 53.0	*Author's conclusions* A combination of HBOT and steroid tx for sudden hearing loss was found to have no significant advantage over steroid tx alone. *Limitations* No blinding, no IT analysis; adequate power although sample size was small, allocation concealment NR; baseline characteristics provided but no analysis of significant differences. *Quality* Fair

Author and Date Study design	Population	Treatment/Outcome Measures	Results	Conclusions Limitations Quality
	Exclusion criteria: Age ≥18 yrs; hx of fluctuant hearing loss; intracranial malignancy; presenting w/ acute neurological symptoms	Results stratified by age	None: 92.5 *P*=NS **Hearing recovery by age** Pts <50 yrs *HBOT* Complete: 52.4% Moderate: 23.9% None: 23.8% *Control* Complete: 58.3% Moderate: 16.7% None: 25% Pts >50 yrs *HBOT* Complete: 58.8% Moderate: 29.4% None: 11.8% *Control* Complete: 22.2% Moderate: 33.3% None: 44.4% *P*=0.05	

Appendix V. Summary of Cost-Effectiveness Studies

Key: ; AUD, Australian dollar; CAD, Canadian dollars; CDSR, Cochrane Database of Systematic Reviews; C/E, cost-effectiveness; COI, conflict of interest; CRD, Center for reviews and Dissemination; C/U, cost-utility; DARE, Database of Abstracts of Reviews of effects ; EuroQoL, measure of health-related quality of life; GBP, British Pound Sterling; grp(s), group(s); HBOT, hyperbaric oxygen therapy; HEED, Health Economics Evaluation Database; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; INAHTA, International Network of Agencies for Health technology Assessment; ITT; intention to treat; LEA, lower extremity amputations; LYG, life-year gained; MSAC, Medical Services Advisory Committee; NHS, National Health Service; NHS EED, National Health Service Economic Evaluation Database; NR, not reported; NZD, New Zealand dollar; ORN, osteoradionecrosis; pt(s), patient(s); QALY, quality-adjusted life-year; QOL, quality of life; RCT, randomized controlled trial; rehab, rehabilitation; RNZN, Royal New Zealand Navy; SD, standard deviation; SIGN, Scottish Intercollegiate Guidelines Network; SR, systematic review; std, standard; tx, treatment (or therapy); tx'd, treated; USD, U.S. dollar; vitD(K), vitamin D(K)

Authors/Objective/Included Studies	Data Sources/Methods	Characteristics of Included Studies	Results	Conclusions/Comments/ Limitations
De Laet et al. (2008) Belgian Health Care Knowledge Center, Brussels, Belgium A systematic review to identify full economic analyses of HBOT and determine the C/E of HBOT compared w/ std care for several indications (includes author/yr/country) MSAC (2003) (Australia) MSAC (2001) (Australia) Hailey et al. (2007) (Canada) Abidia et al. (2003) (UK) Guo et al. (2003) (U.S.) Dempsey et al. (1997) (Canada) Wheen (1994) (New Zealand)	7 included studies (6 C/E analysis, 1 RCT w/ cost estimate comparisons) Indications (relevant to this report) Diabetic foot ulcers; ORN; nondiabetic chronic wounds *Data sources:* INAHTA; MEDLINE; Embase; CRD; DARE; NHS EED; HTA; CDSR; Econlit; manually searching bibliographies Search dates: January 2008 *Inclusion criteria:* No restrictions on either time period or language; full economic evaluations comparing 2 or more alternatives and considering both costs and consequences, including C/E, C/U, or cost benefit analysis, outcomes expressed as costs per LYG,	<u>Abidia (2003)</u> n=18, RCT comparing mean total costs of visits for diabetic ulcer dressing per pt in control w/ costs of HBOT and associated complications <u>Guo (2003)</u> Decision tree analysis calculating costs per QALY for pts w/ severe diabetic foot ulcers tx'd w/ std wound tx vs std wound tx w/ adjunctive HBOT Assumptions: QALYs derived from EuroQoL weights (primarily healed: 0.6; healed w/ minor LEA: 0.6; healed w/ major LEA: 0.31; death: 0); HBOT costs: USD 407/tx; costs for minor LEA: USD 40,673; costs for major LEA $39,404; average # HBOT sessions: 29 Perspective: Payer and societal Time horizon: 1, 5, and 12 yrs Discount rate: 3% Yr for costs: 2001 <u>Hailey (2007)</u> Decision tree analysis calculating costs per QALY for pts w/ diabetic foot ulcers tx'd w/ std wound tx vs std wound tx w/ adjunctive HBOT Assumptions: Base case model parameters were based on 7 controlled trials; QALYs derived from EuroQoL weights (primarily healed: 0.6; healed w/ minor LEA: 0.61; healed w/ major LEA: 0.31;	**Diabetic foot ulcers** <u>Abidia (2003)</u> Mean total cost for ulcer dressing /pt/yr HBOT grp: GBP 1972 Control: GBP 7946 HBOT cost: GBP 3000/pt Potential cost saving: GBP 2960/pt <u>Guo (2003)</u> # major LEA HBOT grp: 205 Control: 50 # major LEA averted due to HBOT: 155 QALY gained yr 1: 50.2 QALY gained yr 5: 265.3 QALY gained yr 12: 608.7 ICER at yr 1: USD 27,310 ICER at yr 5: USD 5166 ICER at yr 12: USD 2255 ICERS were very sensitive to efficacy assumptions and also sensitive to quality weights, # HBOT sessions/case, cost/HBOT and cost of major and minor LEA assumptions (model not robust)	*Author's conclusions* HBOT may be cost effective under very specific assumptions of effectiveness and costs; increased benefits and reduced costs may include reduced hospital stays, reduction in amputations, improved QOL, reduction in outpt care, etc; economic evaluations are currently based on insufficient data and therefore have important limitations for both incremental cost and benefit calculations. *Limitations* Sufficient benefit and cost data are lacking for all examined indications resulting in poor quality evidence; all included studies showed severe limitations for both the incremental cost and for

Authors/Objective/Included Studies	Data Sources/Methods	Characteristics of Included Studies	Results	Conclusions/Comments/ Limitations
	costs per QALY, and any disease specific outcome *Exclusion criteria*: Cost descriptions and cost comparisons Quality assessment tool: Not specified	unhealed w/ no related surgery 0.44; death: 0); HBOT costs: CAD 3652/30 txs; first yr costs for healing CAD 4228 (subsequent yrs CAD 3890); first yr costs for minor LEA CAD10,823 (subsequent yrs CAD 10,484); first yr costs for major LEA CAD 19,195 (subsequent yrs 11,712); first yr costs for unhealed CAD 9386 (subsequent yrs CAD 9428); average # HBOT sessions: 30 Perspective: Ministry for Health Time horizon: 12 yrs Discount rate: NR Yr for costs: adjusted to 2004 CAD <u>MSAC (2001)</u> C/E of monoplace HBOT vs procedures w/o HBOT for diabetic pts and pts w/ ORN Assumptions: Risk for major LEA (based on 5 studies) w/ HBOT, 20% (95% CI 11%-30%); risk for minor LEA (based on 2 studies) 9% (95% CI –8% to 25%);risk difference of ORN among HBOT pts vs controls post tooth extraction (based on 1 study), 24.3% (95% CI 15.9%-47%; costs for 30 HBOT sessions, AUD 6941; costs for all LEA AUD 14,805; costs for minor LEA, AUD 2194; costs for rehabilitation, AUD 8758 Perspective: NR Time horizon: NR Discount rate: NR Yr for costs: NR <u>MSAC (2003)</u> C/E of monoplace HBOT vs procedures w/o HBOT for nondiabetic chronic wounds Assumptions: Mean reduction in wound area w/ HBOT (based on 1 study) 35.7% (SD=17), Mean reduction in wound area w/o HBOT (based on 1 study) 2.7% (SD=11), Perspective: NR Time horizon: NR	<u>Hailey (2007)</u> Adjunctive HBOT was dominant over std care alone QALY gained HBOT grp: 3.64 Control: 3.01 12-yr cost to pt HBOT grp: CAD 40,695 Control: CAD 49,786 Results remained stable in sensitivity analysis robust model) <u>MSAC (2001)</u> Costs/major LEA avoided, AUD 11,142 Costs/any amputation avoided, AUD 22,054 Results were sensitive to the assumptions, particularly # HBOT sessions, efficacy assumptions (model not robust) <u>Wheen (1994)</u> Average cost/ pt HBOT grp at navy hospital: NZD 10,565 HBOT grp at public hospital bed costs: NZD 31,026 Control: NZD 38,359 **ORN** <u>Dempsey (1997)</u> HBOT was dominant over hypothetical control Total tx costs HBOT grp: CAD 10,064/pt Hypothetical control: CAD 63,211/pt Results were sensitive to the	the benefits calculations. *COI* None reported *Quality of review* Good

Authors/Objective/Included Studies	Data Sources/Methods	Characteristics of Included Studies	Results	Conclusions/Comments/ Limitations
		Discount rate: NR Yr for costs: NR Wheen (1994) C/E HBOT to manage diabetic foot ulcers Assumptions: Outcomes based on 1 study; hospitalization costs, NZD 120/d (RNZN hospital, HBOT grp), NZD 450 (public hospital, control grp); amputation costs, NZD 493; costs for prosthesis supply and training, NZD 1300; costs for occupational therapy, NZD 113; costs for physiotherapy, NZD 64; costs for walking frame, NZD 100 costs for crutches, NZD 89 Perspective: NR Time horizon: NR Discount rate: NR Yr for costs: NR Dempsey (1997) C/E of HBOT for ORN of the mandible; hypothetical population of 21 pts Assumptions: pts healed before reconstructive surgery, 65%; pts healed after surgery, 23%; no healing, 12% (range of healing 8%-75%); HBOT costs CAD 350.59/session Perspective: Societal Time horizon: NR Discount rate: 5% Yr for costs: 1995	assumptions, particularly # days in hospital (model not robust) MSAC (2001) ICER/case ORN avoided: AUD 28,480 Upper sensitivity analysis: ICER AUD 16,668 Lower sensitivity analysis: ICER AUD 66,187 Results were sensitive to the assumptions, particularly # HBOT sessions and costs (model not robust) **Nondiabetic chronic wounds** MSAC (2001; 2003) Tx costs for 1/3 reduction in wound area was AUD 6941/pt/30 HBOT sessions C/E for 1 person cured of chronic leg ulcer, AUD 27,764 (*P* value was not significant for effectiveness so low confidence in C/E calculation)	
Ritchie et al. (2008) NHS (UK) A systematic review to determine the C/E of HBOT as mono- or adjunctive tx compared w/ std tx (includes author/yr/country)	8 included studies (3 C/E analysis, 2 cost utility analysis, 3 UK-based cost analysis papers) **See De Laet 2008 for the results of following included studies:** MSAC (2001) (Australia)	Cianci (1990) Nonrandomized trial, including a C/E analysis (n=21; 19%-50% total body surface area burns; HBOT as adjunct to std tx); outcomes, length of hospital stay, # surgical procedures, cost of hospital care Perspective: Health service provider Time horizon: Period of study Discount rate: NA	Cianci (1990) Mean length of stay HBOT grp: 28.4 days (range 13-60) Control: 43.2 days (range 20-81) Mean # surgical procedures HBOT grp: 1.7 (range 0-4) Control: 2.8 (range 0-8) Mean costs of hospital care HBOT grp: USD 60,350 (range USD	*Author's conclusions* All included studies were compromised by sparse and poor quality of clinical effectiveness data and results should be interpreted w/ caution. The results were not robust but should be

Authors/Objective/Included Studies	Data Sources/Methods	Characteristics of Included Studies	Results	Conclusions/Comments/ Limitations
MSAC (2001) (Australia) Hailey et al. (2007) (Canada) Abidia et al. (2003) (UK) Guo et al. (2003) (U.S.) Dempsey et al. (1997) (Canada) Ward et al. (2000) (UK) Cianci et al. (1990) (U.S.) Treweek and James (2006) (UK)	Hailey et al. (2007) (Canada) Abidia et al. (2003) (UK) Guo et al. (2003) (U.S.) Dempsey et al. (1997) (Canada) **Included here:** Ward et al. (2000) UK Cianci et al. (1990) US Treweek and James (2006) UK *Indications (included here):* Thermal wounds; ORN; start-up, annual and per-tx costs of HBOT *Data sources:* NHS EED; HEED; websites of health economics units; hand searching bibliographies of effectiveness data *Search dates:* 2005 – October 2007 *Inclusion criteria:* Any study design; any date; HBOT as mono- or adjunctive tx; adult population; reporting both costs and outcomes of HBOT vs 1 or more alternative std UK txs or placebo; cost analysis studies based on UK settings *Exclusion criteria:* Non-	Yr for costs: 1987 USD <u>Ward (2000)</u> Cost analysis to provide a crude determination C/E of HBOT in the prevention of ORN following dental extraction; hypothetical population of 500,000 w/ 5 pts having undergone radiotherapy tx requiring dental extraction' outcomes, relative costs of HBOT vs non-HBOT for preventing ORN Assumptions: Incidence of ORN following extraction is 5.8%; effectiveness of HBOT in the prevention of ORN is 80%; pts who develop ORN are either tx'd successfully w/ one course of HBOT or progress to the worst-case scenario w/ a pathological fracture of the mandible; the probability of progressing to the worst-case scenario is 55%; worst-case scenario pts will require HBOT and surgery, medication and additional hospital care Perspective: Not specified, assumed to be UK NHS Time horizon: NR Discount rate: NA Yr for costs: NR, assumed 2000 USD <u>Treweek and James (2006)</u> Cost analysis to estimate start-up, annual and per-tx costs of adjunctive HBOT for inpts; primary data gathering over 10 yrs Assumptions: Monochamber in 1 of 6 large Scottish teaching hospitals; inpt hospital costs not included because they would exist independent of the tx; outcomes, lower and upper range costs amortized over 10 yrs Perspective: Not specified, assume to be UK NHS Time horizon: NA Discount rate: 3% and 7% Yr for costs: 2004 USD	27,000-USD 131,000) Control: USD 91,960 (range USD 24,700-USD 210,000) <u>Ward (2000)</u> Expected cost/yr HBOT pathway: GBP 20,000/pt Non-HBOT pathway: GBP 5000/pt Cost of treating the worst-case scenario needs to be GBP 100,000 for the costs of both options to break even; sensitivity analysis found the break-even costs to range from GBP 17,500-GBP 127,500 <u>Treweek and James (2006)</u> Capital costs Lower range costs: GBP 64,800 Upper range costs: GBP 72,000 Staff nurse Lower range costs: GBP 21,978 Upper range Costs: GBP 26,541 Staff consultant Lower range costs: GBP 4880 Upper range Costs: GBP 5333 Oxygen Lower range costs: GBP 6812 Upper range Costs: GBP 11,642 Property and cleaning Lower range costs: GBP 306 Upper range costs: GBP 3848 Miscellaneous Lower range costs: GBP 132 Upper range costs: GBP 141 General overheads Lower range costs: GBP 256 Upper range costs: GBP 312 # of txs/yr	considered as indicative. There is perhaps greater certainty over the direction of benefit in relation to diabetic foot ulcers where all 4 studies were broadly supportive of the C/E of HBOT compared w/ std tx; sensitivity analysis showed that results were particularly sensitive to the efficacy and utility measures used, # HBOTs/pt, # HBOT units in use and amputation costs. *Limitations* Sufficient benefit and cost data are lacking for all examined indications resulting in poor quality evidence; all included studies showed severe limitations for both the incremental cost and for the benefits calculations; Ward (2000) QOL not included in analysis, costs represent very crude estimates. *COI* One author reported receiving <15% of his income through the provision of HBOT. *Quality of review*

Authors/Objective/Included Studies	Data Sources/Methods	Characteristics of Included Studies	Results	Conclusions/Comments/ Limitations
	English language studies; animal studies; narrative reviews; meeting abstracts; editorials etc; pediatric studies Quality assessment tool: Drummond et al. (2001) 10-point checklist		Lower range costs: GBP 600 Upper range costs: GBP 1600 Cost/tx Lower range costs: GBP 32 Upper range costs: GBP 41	Good